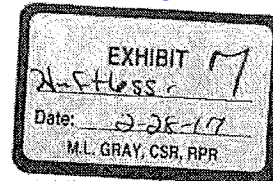


Exhibit A



An Examination of the Causal Association between Olmesartan and Gastrointestinal Adverse Events Resembling Sprue-Like Enteropathy

Prepared by
Susan Hutfless, PhD

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Abbreviations and Definitions

Common abbreviations and definitions used throughout this document

Abbreviations	
AE	Adverse event
ARB	Angiotensin II receptor blocker
ACEI	ACE inhibitor
CI	Confidence interval
CRF	Case report form
CSR	Clinical Study Report
DSI	Daichii Sankyo
EBGM	Empirical Bayes Geometric Mean
EB05	Lower bound of the 2-sided 90% confidence interval of the EBGM
EB95	Upper bound of the 2-sided 90% confidence interval of the EBGM
FDA	Food and Drug Administration (United States)
FAERS	FDA Adverse Event Reporting System
IEL	Intraepithelial lymphocyte
MedDRA	Medical Dictionary for Regulatory Activities

Abbreviations	
NP	Not Performed
NR	Not Reported
OR	Odds Ratio
PMID	PubMed ID
PRR	Proportional Reporting Ratio
RR	Rate Ratio
SOC	System Organ Class
TEAE	Treatment Emergent Adverse Event
U.S.	United States
Definitions	
Hypertension	<p>According to the U.S. National Institutes of Health, hypertension is a condition present when blood flows through the blood vessels with a force greater than normal. Hypertension can strain the heart, damage blood vessels, and increase the risk of heart attack, stroke, kidney problems, and death. About 3 million Americans have high blood pressure.[PubMed Health Glossary]</p> <p>Hypertension is often called high blood pressure.</p>
Celiac disease	<p>An immune-mediated sensitivity to gluten that results in damage to the intestinal villi, contributing to malabsorption and gastrointestinal disorders. Symptoms include diarrhea and weight loss. The diagnosis of celiac disease involves serologic testing for immunoglobulin A tissue transglutaminase antibodies (IgA tTGA). Maintaining a gluten-free diet results in the resolution of symptoms and intestinal inflammation.</p> <p>Celiac disease is sometimes called celiac sprue.</p>
Drug-induced enteropathy	<p>Damage to the intestinal villi as a result of a pharmaceutical agent instead of gluten. According to the Bucharest algorithm to diagnose microscopic colitis, symptoms response after withdrawal of the drug is sufficient to diagnose drug-induced enteropathy.[Rostami 2015]</p> <p>Drug-induced enteropathy is sometimes called sprue-like enteropathy.</p>
Olmesartan-induced enteropathy	<p>Drug-induced enteropathy as a result of olmesartan. The Bucharest algorithm specifically mentions olmesartan-induced enteropathy as a form of enteropathy that can be diagnosed based on symptom response after drug withdrawal.[Rostami 2015]</p>
Dechallenge	<p>Withdrawal of a suspect product from a patient's therapeutic regimen. [U.S. FDA 2001] The FDA defines positive dechallenge as "partial or complete disappearance of an adverse experience after withdrawal of the suspect product".[U.S. FDA 2001] Evidence of positive dechallenge is considered by the FDA to suggest a causal relationship between the use of a product and the adverse event.[U.S. FDA 2005] "In assessing case reports, FDA recommends that sponsors look for features that may suggest a causal relationship between the use of a product and the adverse event, including: Evidence of positive dechallenge or positive rechallenge." [U.S. FDA 2005]</p>

Abbreviations	
Rechallenge	<p>Reintroduction of a suspect product suspected of having caused an adverse experience following a positive dechallenge.[U.S. FDA 2001] The FDA defines positive rechallenge as "reoccurrence of similar signs and symptoms upon reintroduction of the suspect product". Evidence of positive rechallenge is considered by the FDA to suggest a causal relationship between the use of a product and the adverse event.[U.S. FDA 2005] "It is possible that even a single well documented case report can be viewed as a signal, particularly if the report describes a positive rechallenge or if the event is extremely rare in the absence of drug use," [U.S. FDA 2005]</p>
Empirical Bayes Geometric Mean (EBGM)	<p>EBGM values indicate the strength of the reporting relationship between a particular drug and event pair. These values are adjusted for age, sex and calendar year to account for differences in relative reporting ratios by these categories. EBGM uses DuMouchel's Multi-item Gamma Poisson Shrinker (MGPS), a disproportionality method that utilizes an empirical Bayesian model to detect the magnitude of drug-event associations in drug safety databases.</p> <p>The EBGM compares the observed reports with the expected. The expected value is calculated by multiplying the proportion of all reports for the drug (i.e., 1% of all reports are for drug X) by the proportion of all reports for the event (i.e., 2% of all reports are for headache). In this example the expected value (1% x 2%) is compared with the observed number of reports by dividing the observed value by the expected value.</p> <p>An EBGM of 1 indicates no association. Values greater than 1 indicate that the event is reported more commonly for the drug than for other drugs. Values less than 1 indicate that the event is reported less often for the drug than other drugs.</p> <p>Using this method adjusts for multiplicity and controls false positive (Type I) errors, by systematically "shrinking" observed-expected ratios that cannot be precisely estimated because of small counts towards 1 (no association). The fewer events there are, the greater the shrinkage. Calculations for rare events (fewer than three events reported for the drug) are shrunk a large amount, while drug-event combinations with 20 or more events are shrunk by a small amount.</p> <p>The FDA calculates the EBGM as part of its internal data mining program [U.S. FDA 2015]</p>
EB05	<p>Lower bound of the 2-sided 90% confidence interval of the EBGM. EB05 greater than or equal to 2 is frequently used as a threshold to define a signal.[Levine 2006]</p>
EB95	<p>Upper bound of the 2-sided 90% confidence interval of the EBGM.</p>

Abbreviations	
Confidence interval (CI)	<p>An indicator of the precision of an effect estimate, such as the EBM. The values contained within the confidence interval represent a range of estimates expected to occur if the same value had been calculated numerous times. For a 90% confidence interval, if the same value was calculated repeatedly from the population of all potentially observable scenarios, about 90% of these intervals would contain the true effect estimate.</p> <p>The confidence interval is affected by the sample size observed. As the sample size increases (i.e., better represents the potentially observable population) the confidence intervals are closer in value to the effect estimate. Regardless of the width of the confidence interval, the best estimate of the relationship between a drug and event is the effect estimate (i.e., EBM).</p>
Effect estimate	A quantitative measure of the strength of a phenomenon. The larger the value, the stronger the effect. Also known as effect size.
Medical Dictionary for Regulatory Activities, MedDRA	MedDRA is a standardized medical terminology to facilitate sharing of regulatory information internationally for medical products used by humans. It was developed by the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). MedDRA can be used in the registration, documentation and safety monitoring of medical products in the pre-marketing and post-marketing periods. FAERS uses MedDRA terminology to classify events. These include specification of adverse events at a specific level (such as the preferred term) and at higher levels including system organ class (SOC). [MedDRA 2013]
Proportional Reporting Ratio, PRR	A commonly used measure of disproportionality (the number of reports in a spontaneous report database for a specific event reported for a particular drug with the number expected based solely on the other reporting in the same database). The PRR is the ratio of the number of reports for the drug-adverse event of interest divided by the total of all reports for the adverse event over the proportion of drug-adverse event reports for the drug not of interest divided by the total of all reports for other adverse events. In a 2x2 framework this equates to $(a/[a+b])/(c/[c+d])$. [Andrews 2014]

Summary of Opinions

The opinions I provide in this report are given to a reasonable degree of scientific certainty and are based on my knowledge, skills, experience and the information available to me at the time these opinions were rendered. If additional information becomes available, I may supplement my opinions to reflect such additional information.

As described in the *Causality Assessment* section of this report, I based my determination of causality using a defined framework. The criteria used and the evidence in support or against those criteria are provided in the Summary Table. In conclusion, I am of the opinion, to a reasonable degree of scientific certainty, that the evidence is sufficient to establish a causal relationship between olmesartan-containing products (hereafter referred to as olmesartan) and gastrointestinal adverse events resembling sprue-like enteropathy (hereafter referred to as enteropathy or olmesartan-induced enteropathy).

By 2006 there was evidence of a causal relationship between olmesartan and enteropathy based on eight cases of enteropathy confirmed by a clinical expert, which included serious cases with positive rechallenge and a description of celiac disease, diarrhea or vomiting, as is consistent with the Bucharest criteria.[Rostami 2015] The clinical expert is a practicing gastroenterologist who has expertise in celiac disease and who has diagnosed patients with olmesartan-induced enteropathy in his practice. These cases were identified from MedWatch forms generated by the manufacturer in response to reports of adverse events related to the symptoms associated with enteropathy by consumers or health care professionals. All of the clinician confirmed cases had a positive rechallenge documented on their MedWatch form. According to the FDA: "It is possible that even a single well documented case report can be viewed as a signal, particularly if the report describes a positive rechallenge or if the event is extremely rare in the absence of drug use." [U.S. FDA 2005] Using the WHO assessment of causality, all eight cases were identified as probably or definitely related to olmesartan.

The PRR and EB05 from the disproportionality analyses in FAERS indicate a signal consistent with the MedWatch case reports. Four different searches were used to identify cases of olmesartan-induced enteropathy using the PRR and EB05. Depending on the outcome definition, the signal could be identified as early as 2005 (all cases of celiac disease: $n=3$, $PRR=9.85$, $\chi^2=15.9$), in 2006 (serious cases of celiac disease: $n=3$, $PRR=10.5$, $\chi^2=17.1$; serious cases of diarrhea with concomitant weight loss or dehydration and positive rechallenge: $n=3$, $PRR=28.2$, $\chi^2=53.9$) or as late as 2007 (serious cases of diarrhea with concomitant weight loss or dehydration [no rechallenge requirement]: $n=17$, $PRR=2.39$, $\chi^2=12.4$). In December 2009, the manufacturer used the PRR (as estimated by the OR) as the sole disproportionality measure in its query of FAERS for celiac disease and identified a signal ($PRR=23.36$) (*Attachment in email communication from Herve Caspard to Allen Feldman dated December 21, 2009; OLM-DSI-0001823413*). An early signal was also detected in my analysis using the EB05, a more conservative measure, and is described later in the text.

Best practices in pharmacoepidemiology recommend following up on signals from spontaneous reporting systems such as FAERS. [Strom 2012][ICH 2004] The ICH Harmonised Tripartite Guideline describes study designs that a manufacturer can pursue after the detection of a signal in a resource such as FAERS.[ICH 2004] There is no evidence that the manufacturer conducted a study to follow up on the signal detected in FAERS of an association between olmesartan and celiac disease.

The other source of information on adverse events is clinical trials. It is my opinion, to a reasonable degree of scientific certainty, that Daiichi Sankyo's clinical trials were inadequately designed and conducted and insufficiently powered to detect a rare event like enteropathy. Despite the limitations in the clinical trials there was a case identified as olmesartan-induced enteropathy by the clinical expert (Study: SE-866/44, Patient no. 1630007, Random no. 4790, Centre no. 1630). In the MedWatch form generated by the manufacturer, there is clear evidence of a positive dechallenge and rechallenge (MFR#SP-2006-003369).

Had the manufacturer taken note of this adverse event from their ROADMAP trial in combination with the positive rechallenge cases that the manufacturer had reported in FAERS, best practices in pharmacovigilance required further investigation into the association between olmesartan and the symptoms of enteropathy. The manufacturer received the report of Patient no. 1630007 on December 5, 2006. The timing of this case is consistent with the identification of

the causal relationship between olmesartan and enteropathy from the MedWatch forms and the signal from the disproportionality analyses in FAERS.

The causal relationship between olmesartan and enteropathy is also supported by information identified in a search of the literature. At the time of the writing of this report, there were 179 cases of olmesartan-induced enteropathy published in case reports. Nearly 80% of these cases had documentation of dechallenge in the publications. Evidence of positive dechallenge is considered by the FDA to suggest a causal relationship between the use of a product and the adverse event.[U.S. FDA 2005] A landmark epidemiology study on the association between olmesartan and malabsorption and celiac disease performed by employees of the French National Health Insurance Fund and a public hospital in Paris identified a strong relationship between olmesartan and these outcomes after accounting for confounding factors.[Basson 2016] Compared with ACEIs (another drug used for hypertension), olmesartan was associated with a greater than 10 times increased relative rate of hospitalizations for malabsorption and celiac disease with greater than 2 years of use. For the other ARBs there was no increase in the rate of hospitalizations for malabsorption or celiac disease after 2 years of use.

In summary, it is my opinion, to a reasonable degree of scientific certainty, that there is sufficient evidence to establish a causal relationship between olmesartan and enteropathy. There is consistent evidence from the MedWatch case reports and signals from FAERS that this causal association was established in 2006.

Summary Table of Information Supporting a Causal Relationship between Olmesartan and Enteropathy

Characteristic	Definition	Sources	Assessment
Characteristics common to causality assessment frameworks			
Temporality	Exposure to an olmesartan-containing product must precede enteropathy	Medwatch case reports Literature case reports FAERS Non-randomized studies Randomized trials	There is evidence from MedWatch case reports, literature case reports and a large claims-based study that the symptoms of enteropathy came after the start of treatment with an olmesartan-containing product. The MedWatch forms and literature case reports provide dates of medication use and dates of outcomes. Only those cases with a temporal relationship were included in this report. The 60 MedWatch cases identified by the clinical expert and 179 cases reported in the literature meet the temporality requirement. The French epidemiology study required a full year of follow-up without a diagnosis associated with malabsorption (including celiac disease) and without a prescription for an assessed anti-hypertensive

Characteristic	Definition	Sources	Assessment
			<p>medication before individuals could contribute information. The authors concluded: "Compared with ACEI, the adjusted rate ratio of hospitalization with a discharge diagnosis of intestinal malabsorption was 2.49 (95% CI 1.73 to 3.57, $p < 0.0001$) in olmesartan users." "Compared with ACEI, the adjusted rate ratio of hospitalization for coeliac disease was 4.39 (95% CI 2.77 to 6.96, $p < 0.0001$) in olmesartan users and increased with treatment duration." [Basson 2016]</p> <p>Individuals with malabsorption disorders were excluded from randomized trials. The cases identified during the randomized trials took olmesartan prior to the onset of symptoms of enteropathy.</p>
Dechallenge	Partial or complete disappearance of an adverse experience after withdrawal of the suspect product	Medwatch case reports Literature case reports	All MedWatch cases and 141 literature cases documented a positive dechallenge. This includes resolution for symptoms of enteropathy after discontinuing use of olmesartan. Evidence of positive dechallenge is considered by the FDA to suggest a causal relationship between the use of a product and the adverse event.[U.S. FDA 2005]
Rechallenge	Re-occurrence of similar signs and symptoms upon reintroduction of the suspect product	Medwatch case reports Literature case reports	All 60 MedWatch cases and 10 literature cases documented a positive rechallenge. Evidence of positive rechallenge is considered by the FDA to suggest a causal relationship between the use of a product and the adverse event.[U.S. FDA 2005]
Bradford-Hill Criteria			
Consistency	Is the exposure-outcome relationship observed in multiple studies?	Medwatch case reports Literature case reports FAERS Randomized trials Non-randomized studies	<p>The exposure-outcome relationship has been observed in Medwatch and literature cases, FAERS, a case who developed the event during a randomized trial and a large, well-conducted retrospective study.</p> <p>The randomized trials were not designed in a way to observe</p>

Characteristic	Definition	Sources	Assessment
			olmesartan-induced enteropathy. None of the trials reported on olmesartan-induced enteropathy in the publications presenting the results to the public or in their clinical trial reports. However, 2 out of the 60 MedWatch cases came from clinical trials (MFR# DSM-2008-00607, SP-2006-003369).
Strength	What is the strength of the association based on the observed effect estimates?	FAERS Randomized trials Non-randomized studies	<p>There was a consistently elevated association between olmesartan and olmesartan-induced enteropathy beginning in 2006 in FAERS (PRRs>10 for all celiac disease and serious celiac disease).</p> <p>As described in Temporality, the French epidemiology study observed that olmesartan was associated with a 2 times increased rate of malabsorption and a 4 times increased rate of celiac disease compared with ACEIs.[Basson 2016] Individuals with greater than 2 years of use had 10 times increased rates of malabsorption and celiac compared with ACEI users.</p> <p>There were no randomized trials specifically designed or with sufficient statistical power to assess the strength of the relationship.</p>
Specificity	Can factors other than the exposure under investigation lead to the outcome?	MedWatch case reports FAERS Non-randomized studies FDA	<p>Other medications and gluten can lead to the enteropathy.</p> <p>The WHO causality assessment of Certain requires that all other medications, comorbidities and allergies have been ruled out as contributing to the adverse event. 24 Medwatch forms met this criteria based on my application of the criteria.</p> <p>Olmesartan is unique among the ARBs to cause enteropathy. There was no signal for the other ARBs identified in FAERS. There was not</p>

Characteristic	Definition	Sources	Assessment
			<p>an elevated effect estimate for other ARBs versus ACEIs in the French epidemiology study.[Basson 2016]</p> <p>According to the FDA "the other 7 ARBs do not appear to demonstrate evidence for an ARB-induced sprue-like enteropathy." (Tracked Safety Issue (TSI) Integrated Review Memorandum May 14, 2013 authored by Susan Lu, R.Ph). The FDA's Safety Communication contains similar language. [U.S. FDA 2013b]</p>
Temporality	Does the cause precede the effect?	<p>Medwatch case reports</p> <p>Literature case reports</p> <p>FAERS</p> <p>Non-randomized studies</p> <p>Randomized trials</p>	As stated above, there is an established temporal relationship.
Biologic gradient (Dose-response)	Is increased exposure associated with a greater likelihood of the outcome?	<p>MedWatch case reports</p> <p>Randomized trials</p> <p>Non-randomized studies</p>	There is insufficient information to make a judgement on a dose-response relationship.
Plausibility	Is the association consistent with other knowledge including mechanism of action and animal experiments?	Literature	<p>A mechanism of action has been proposed. Olmesartan-induced enteropathy has been demonstrated in experiments on rats.</p> <p>"Olmesartan-associated enteropathy shares many features with coeliac disease, including symptoms and immunopathogenic pathways, such as increased numbers of CD8+ cells and corresponding overexpression of IL15 by epithelial cells. Taken together, the treatment of epithelial cells with olmesartan medoxomil induces a response by intestinal epithelial cells that is similar to the innate effects of gluten upon the epithelium of coeliac patients."[Marietta 2015]</p> <p>Olmesartan induced enteropathy exists in rats.[de Araújo 2015]</p>

Characteristic	Definition	Sources	Assessment
Coherence	Are laboratory experiments and epidemiologic studies consistent?	Literature Non-randomized studies	Both laboratory experiments and epidemiologic studies have demonstrated an association between olmesartan and enteropathy.[Marietta 2015] [de Araújo 2015][Basson 2016]
Experiment (or natural experiment)	Does removing the exposure end the symptoms associated with the outcome or lead to a reduction in disease risk? Does adding back the exposure lead to a recurrence of the outcome?	Medwatch case reports Literature case reports	See dechallenge and rechallenge. There have been numerous natural experiments that support that symptoms decrease when olmesartan is discontinued and reappear when olmesartan is reintroduced. This includes 60 MedWatch cases. Eighty percent of literature cases had positive dechallenge and 10 literature cases had documented rechallenge.
Analogy	Are there other instances of similar exposure-outcome relationships.		Drug-induced enteropathy exists for other medications.[Podolsky 2015]

Background and Experience of Dr. Susan Hutfless

I am an epidemiologist specializing in examining the causes and treatments of gastrointestinal disorders. I have over 10 years of experience conducting epidemiologic research related to gastroenterology. I received a Bachelor of Arts degree in Psychology from Creighton University in 2002; a Master of Science degree in Epidemiology from the Harvard School of Public Health in 2006; and a PhD in Epidemiology from the Johns Hopkins School of Public Health in 2010. I am currently an Assistant Professor of Medicine in the Gastroenterology Division of Johns Hopkins University where I am the Director of the Gastrointestinal Epidemiology Research Center and a member of the Center for Drug Safety & Effectiveness. I conduct research funded by the National Institutes of Health and the Agency for Healthcare Research and Quality and have authored multiple peer-reviewed publications that have been published in journals such as *Gastroenterology*, *Annals of Internal Medicine*, *JAMA* and *BMJ*. I lead the Inflammatory Bowel Disease Workgroup of the American Gastroenterology Association's (AGA) Quality Measures Committee. The AGA is a leading organization of gastroenterologists nationally and internationally with over 16,000 members.

I am associated with two groups respected for their expertise in systematic reviews. I am a contributor to the Cochrane collaborative which is known internationally for producing high quality systematic reviews. I am a core faculty member of the Johns Hopkins Evidence-based Practice Center which performs comparative effectiveness reviews and other data syntheses (i.e., topic development documents and topic briefs) on behalf of the U.S. Agency for Healthcare Quality & Research. These reviews have been cited in treatment guidelines and have received media coverage. My expertise as a systematic reviewer led to an invitation to conduct a review on smoking and inflammatory bowel disease for the 2014 U.S. Surgeon General's Report on Smoking [U.S. Department of Health and Human Services 2014]. I use a causality assessment framework in this report that is consistent with that used in my chapter of the Surgeon General's Report.

A copy of my CV is included (Appendix). I charged \$500 per hour for work my as an expert in this case.

What is Epidemiology?

Epidemiology is the study of the distribution and determinants of disease in human populations. Epidemiologists examine how often a disease occurs and what factors are associated with differences in rates of disease occurrence. The branch of epidemiology focused on studying drugs is called pharmacoepidemiology. Pharmacoepidemiology is the study of the use of drugs including assessments of benefits and risks [Johns Hopkins General Internal Medicine 2016]. Pharmacovigilance is defined as the study of the "safety of marketed drugs under practical conditions of clinical use in large communities" [Andrews 2014].

Epidemiologists have developed tools to make causal assessments of the association between a factor and disease occurrence for single cases. According to the leading textbook on Pharmacoepidemiology [Strom 2006] [Strom 2012]:

Case reports are useful for raising hypotheses about drug effects, to be tested with more rigorous study designs. However, in a case report one cannot know if the patient reported is either typical of those with the exposure or typical of those with the disease. Certainly, one cannot usually determine whether the adverse outcome was due to the drug exposure or would have happened anyway. As such, it is very rare that a case

report can be used to make a statement about causation. One exception to this would be when the outcome is so rare and so characteristic of the exposure that one knows that it was likely to be due to the exposure, even if the history of exposure were unclear.

Case reports can be particularly useful to document causation when the treatment causes a change in disease course which is reversible, such that the patient returns to his or her untreated state when the exposure is withdrawn, can be treated again, and when the change returns upon repeat treatment. This type of challenge - re-challenge situation is relatively uncommon, however, as physicians generally will avoid exposing a patient to a drug if the patient experienced an adverse reaction to it in the past.

The stronger the drug-event relationship in each case and the lower the incidence of the adverse event occurring spontaneously, the fewer case reports are needed to perceive causality. It has been found that for rare events, coincidental drug-event associations are so unlikely that they merit little concern, with greater than three reports constituting a signal requiring further study. In fact, it has been suggested that a temporal relationship between medical product and adverse event, coupled with positive de-challenge and re-challenge, can occasionally make isolated reports conclusive as to a product-event association.

Because enteropathy is rare, this report will closely examine case reports to determine causality. The information from case reports and studies, including an epidemiologic study, are combined to evaluate the body of evidence and make a determination of a causal relationship.

Key Events

1. Olmesartan is an angiotensin II receptor blocker (Table 1). This class of drugs is also called angiotensin II receptor antagonists, or angiotensin II receptor inhibitors. Olmesartan medoxomil was approved by the FDA for the treatment of hypertension in April 2002 and is marketed by the manufacturer, Daiichi Sankyo, as Benicar. Formulations of olmesartan combined with other anti-hypertensives were approved by the FDA in 2003 (Benicar HCT; combination with hydrochlorothiazide), 2007 (Azor; combination with amlodipine besylate) and 2010 (Tribenzor; combination with hydrochlorothiazide and amlodipine besylate). Since 2006, over 1 million Americans per year have filled a prescription for an olmesartan-containing product. [U.S. FDA 2011A; U.S. FDA 2013b; U.S. FDA 2014]
2. The first case reported by the manufacturer to the FDA of serious gastrointestinal symptoms associated with a dechallenge and rechallenge of olmesartan was in August 2004 (MFR#SU-2004-002638).
3. In June 2009, the manufacturer submitted an Annual Periodic Adverse Drug Experience Report on events occurring from April 26, 2008 through April 25, 2009. The manufacturer identified adverse events among those currently on the drug's label and those considered unlabeled. Two percent of the serious, unlabeled cases were identified as celiac disease. In November 2009, the FDA requested that the manufacturer review its cases of celiac disease.
4. In response to FDA's 2009 request, Daiichi provided a report on January 14, 2010 (OLM-DSI-0001247409-541: Celiac Disease And Olmesartan Medoxomil - An Analysis of the Daiichi Sankyo Global Safety Database, January 13, 2009).

- a. They identified 43 reports of adverse events coded with the term "celiac disease" in their global safety database, including 16 out of 17 cases with a positive rechallenge.
 - b. They summarized the findings from their clinical trials but limited the search to celiac disease. They did not investigate symptoms associated with celiac disease or enteropathy. They stated their findings as: "No serious case of new-onset celiac disease was observed in any of the clinical studies investigating olmesartan medoxomil that have now enrolled a consolidated population in excess of 22,876 patients. There is one clinical study serious adverse event that describes a recrudescence of celiac disease complaints within the first 10 days of treatment with olmesartan medoxomil 10 mg in a 70-year-old woman previously diagnosed with celiac disease." (MFR#DSM-2009-00672)
 - c. Both cases of olmesartan-induced enteropathy that were instigated during clinical trials (MFR# DSM-2008-00607, SP-2006-003369) had been identified by the manufacturer prior to 2009. The MedWatch forms associated with these cases describe positive dechallenge and rechallenge.
5. In June 2012, a series of 22 cases of sprue-like enteropathy associated with olmesartan were published online. [Rubio-Tapia 2012] According to the case series:
- All 22 patients included in this report were seen at Mayo Clinic in Rochester, Minnesota, between August 1, 2008, and August 1, 2011, for evaluation of unexplained chronic diarrhea and enteropathy while taking olmesartan. Celiac disease was ruled out in all cases. To be included in the study, the patients also had to have clinical improvement after suspension of olmesartan.*
- The cases were 59% women and the average age was 69.5 years. Eighteen of the 22 patients had a biopsy after they stopped taking olmesartan and all had histologic recovery or improvement. The authors concluded that "Olmesartan may be associated with a severe form of sprue-like enteropathy. Clinical response and histologic recovery are expected after suspension of the drug." [Rubio-Tapia 2012] Since that time, the 2015 Bucharest Consensus on the diagnosis of microscopic colitis stated that milder forms of enteropathy may also be associated with olmesartan. [Rostami 2015]
6. Subsequent to the publication of the case series, FDA requested that the manufacturer provide a review of "all serious spontaneous post-marketing reports of malabsorption, enteropathy, microscopic colitis, celiac-like symptoms, or chronic diarrhea with clinically significant weight loss associated with olmesartan." (OLM-DSI-0001247624-626)
7. In response to the FDA's request, Daiichi Sankyo submitted a report on September 28, 2012, describing a total of 80 adverse event reports in its global safety database, including 28 out of 29 cases with positive rechallenge information (OLM-DSI-0001247409-541).
8. As part of the FDA's analysis of FAERS, a signal between Benicar and malabsorption resulting in severe diarrhea and weight loss was reported in the FDA's April – June 2012 quarterly report of Potential Signals of Serious Risks/New Safety Information.
- a. Based on the FAERS findings, a distributed database package was sent to Mini-Sentinel (the precursor to Sentinel) to evaluate an association between olmesartan and malabsorption. Two analyses were performed. In the June 2013 analysis, candesartan, eprosartan, irbesartan, losartan, olmesartan, telmisartan, valsartan, hydrochlorothiazide, atenolol and amlodipine monotherapy were examined for diagnosis of celiac disease (ICD-9-CM 579.0) in an inpatient, outpatient or emergent setting. An interim analysis had included candesartan, eprosartan, irbesartan, losartan, olmesartan, telmisartan and valsartan monotherapy and their combination with hydrochlorothiazide for diagnosis of celiac disease in an inpatient or outpatient setting. [U.S. FDA 2012]

- b. In June 2013 the results were posted.[U.S. FDA 2013a] The time period examined was 2007-2011 and all individuals were required to have 365 days of follow-up without any contributing medication prior to the first use of the medication to contribute (i.e., 365 wash-out period) and be considered new users. The majority of patients who used each medication were aged 45-64 years old. Numbers of male and female medication initiators were roughly equal, although women appeared to be more likely to have longer periods of adherence (730-Day Min Episode Duration and Blackout Period). The new users and days at risk varied by medication. Eprosartan had the fewest new users (258) and shortest number of days at risk (40,855). Amlodipine had the largest number of new users (991,184) and days at risk (243,023,217). Olmesartan had 151,461 new users contributing 21,816,716 days at risk. A subset of 4,419 new users had a minimum 730 days of exposure to olmesartan (4,358,523 days at risk). The analyses did not account for differences in age, sex or other factors. The FDA Safety Communication interpreted the results of the Mini-Sentinel Analyses [U.S. FDA 2013b]:

The signal of sprue-like enteropathy with olmesartan was further investigated for a possible ARB class effect using active surveillance data. Mini-Sentinel and CMS Medicare data were assessed for celiac disease (as a marker for enteropathy and other gastrointestinal symptoms) after exposure to ARBs. Mini-Sentinel and CMS Medicare assessments of ICD-9 codes for celiac disease showed that at a 2-year minimum exposure, which correlates with the long latency observed in literature and case reports, olmesartan users had a higher rate of celiac disease diagnoses in claims and administrative data than users of other ARBs. Interpretation is limited by the small number of events observed at longer exposure periods and the uncertainty about the validity of codes for celiac disease, but these results support other data in suggesting a lack of a class effect.

9. In July 2013, a Drug Safety Communication was issued and the olmesartan label was changed to include intestinal symptoms with specific reference to sprue-like enteropathy. [U.S. FDA 2013b] The FDA noted the specificity of olmesartan with the outcome compared with the other drugs in its class "Sprue-like enteropathy has not been detected with ARB drugs other than olmesartan."
10. Adverse events consistent with the symptoms of enteropathy are the most strongly associated events in FAERS for olmesartan as of the first quarter of 2016. Based on a query of all adverse events associated with an olmesartan-containing product, the highest EBGM and EB05 values were associated with sprue-like enteropathy terms (i.e., intestinal villi atrophy, malabsorption). The values exceeded 100 for both the EBGM and EB05.

Causality Assessment

I have reviewed the available data regarding the safety of olmesartan-containing products with respect to olmesartan-induced enteropathy. I will offer opinions regarding exposure to olmesartan-containing products and risk of signs and symptoms of olmesartan-induced enteropathy. I have not systematically reviewed the data regarding the efficacy of olmesartan-containing products, and will not be offering opinions on this issue.

The standard definition of causality as it relates to non-infectious diseases identifies causal components which together lead to disease. Once a combination of components sufficient to cause disease are present, the disease occurs. A component that is always required to cause disease is called a necessary cause. The components may differ between individuals to create a sufficient cause. For example, smoking is known to be associated with lung cancer. Smoking is not a sufficient cause as not all individuals who smoke develop lung cancer. Smoking is not a necessary cause because some individuals who do not smoke develop lung cancer (*i.e.*, radon exposure). According to the United States Centers for Disease Control & Prevention "Public health action does not depend on the identification of every component cause. Disease prevention can be accomplished by blocking any single component of a sufficient cause, at least through that pathway." [CDC 2012]

In the setting of this investigation, my aim is to examine if olmesartan is a component cause of symptoms with what is now often referred to as olmesartan-induced enteropathy. There is consensus that olmesartan causes enteropathy. The gastroenterology community recognizes olmesartan in a key textbook where olmesartan is listed in the section "Drugs Causing Malabsorption". [Podolsky 2015] The pathology community also recognizes olmesartan. There is a chapter devoted to "Olmesartan Enteropathy" in a textbook on diagnostic gastrointestinal pathology. [Greenston 2015] However, because this terminology came into use after the acceptance of this association, I will examine other conditions and symptoms associated with enteropathy. These include celiac disease, which was used in the Mayo Clinic case series, diarrhea, weight loss, dehydration and vomiting. These symptoms were identified in consultation with Daniel Leffler, MD, a gastroenterologist with clinical expertise in celiac disease and its pathogenesis.

A commonly used and generally accepted methodology in epidemiology to assess causality for non-infectious exposure-outcome relationships is the Bradford-Hill criteria or concepts (Table 2). [U.S. Department of Health and Human Services 2004] This methodology has been used in the United States' Surgeon General's Reports to make decisions regarding scientific consensus. [U.S. Department of Health and Human Services 2014] Important components common to the Bradford-Hill criteria and the features that the FDA recommends that sponsors use to make decisions about causality include temporality, dechallenge and rechallenge. [U.S. FDA 2005] The concepts of temporality, dechallenge and rechallenge are common to most causality assessments. [Strom 2006] [Strom 2012] Koch's postulates, a list of criteria created in the 1890s to assess causality, includes dechallenge and rechallenge as two of the four criteria to assess the relationship between microorganisms and disease (the other two criteria are related to specificity and the ability to grow the microorganism in culture). [Andrews 2014] Mann's Pharmacovigilance, a leading pharmacoepidemiology textbook, identifies temporality, dechallenge and rechallenge as particularly important with respect to causality assessment: "In fact, it has been suggested that a temporal relationship between a medical product and adverse event, coupled with positive de-challenge and re-challenge, can occasionally make isolated reports conclusive as to a product—event association". [Andrews 2014]

In order to come to a conclusion on the causal relationship between olmesartan-containing products and olmesartan-induced enteropathy, I will review the evidence taking into account the consistency of associations across the different information sources with particular emphasis on temporality, dechallenge and rechallenge. I will then assess the evidence using the Bradford-Hill criteria and make a causal determination.

Objectives

The overarching goal of this assessment is to examine the causal association between olmesartan and gastrointestinal adverse events associated with olmesartan-induced enteropathy among adults aged 18 and older. The association between olmesartan and the adverse events will be examined systematically by pursuing three sources of information:

- 1) Review of a selection of MedWatch forms reported by the manufacturer to the FDA.
 - a. I reviewed a selection of MedWatch forms identified by the clinical expert. He selected serious cases of celiac, vomiting or diarrhea and positive rechallenge, symptoms which he considered relevant to diagnosis of olmesartan-induced enteropathy.
- 2) Review of the association between olmesartan and the adverse events reported to FAERS.
 - a. Based on a conversation with the clinical expert, I chose to examine cases of celiac disease and diarrhea that occurred with either weight loss or dehydration. These symptoms were selected to identify cases of chronic diarrhea. There is no MedDRA preferred term for chronic diarrhea.
- 3) Systematic review of the published literature.
 - a. I aimed to identify case reports from the literature in addition to randomized and non-randomized studies reporting on olmesartan-induced enteropathy or its symptoms.

The information from the Medwatch forms (temporality, dechallenge, rechallenge, consistency, specificity, temporality, biologic gradient, experiment), FAERS (consistency, temporality, strength, specificity) and the articles identified in the systematic review including case reports (temporality, dechallenge, rechallenge, consistency, temporality, biologic gradient, experiment), randomized trials (consistency, strength, temporality, biologic gradient) and non-randomized studies (consistency, strength, specificity, temporality, biologic gradient, coherence) were used in combination with other information from the literature, as needed, to make a causal determination.

I will provide an opinion on when there was sufficient information to determine a causal relationship between olmesartan and enteropathy.

The methods and results of each information source will be reported followed by the causal assessment.

Objective 1. Review of a Selection of Medwatch Forms Reported by The Manufacturer to The FDA.

Methods

Identification of cases. I received MedWatch forms determined by the clinical expert to be cases consistent with olmesartan-induced enteropathy based on descriptions of diarrhea, vomiting or celiac disease in the preferred terms or the text description of the event, that were also serious and showed a rechallenge (consistent with the Bucharest criteria). [Rostami 2015]

Review of case forms to assess causality. I used the World Health Organization (WHO)-Uppsala Monitoring Center causality assessment system to determine causality. The WHO system emphasizes temporality, dechallenge, rechallenge and alternative causes to assess causality (Table 3). [Uppsala Monitoring Center] To make case by case causality assessment, I asked the clinical expert to assess olmesartan dechallenge and rechallenge and the role that concomitant comorbidities, medications, and allergies played in the development of the adverse event as he reviewed each MedWatch form. The clinical expert had access to source files underlying each form which he could also use to help make his determinations. I did not inform him that his determinations on the role of concomitant comorbidities, medications or allergies would be used for causality assessment. If the comorbidities, medications and allergies were thought to not contribute, no suspect drugs other than an olmesartan-containing product were listed; and no other drugs were listed then the assessment was that the event could not be explained by alternative diseases or medications.

The questions related to dechallenge and rechallenge from the Naranjo scale were used, [Naranjo 1981] I confirmed that all cases identified by the expert met the criteria of temporality based on the dates of olmesartan start and outcome listed on the MedWatch forms (temporality is required for the WHO assessment and Naranjo). (The complete Naranjo assessment was not applicable due to the lack of specificity of common gastrointestinal symptoms such as diarrhea (preventing an assessment of alternative causes and past history of the event), the rarity of the event, the lack of trials designed specifically to assess this safety outcome (preventing an assessment of reaction with placebo), the lack of applicability of a test for drug toxicity, poor reporting on dose or changes in dose (assessment of dose response), and an expected absence of information to confirm objective evidence.)

Causality assessment. A WHO determination of "certain" was made if temporality existed, alternative causes could not explain the event, and there was a positive dechallenge and rechallenge. If other drugs were listed but were not thought to contribute, no other suspect drugs were listed, and there was a positive dechallenge then the event was considered probable. If the event was not considered certain or probable, but temporality was met, the association was listed as possible. Events with unclear temporality were excluded, thus no events were considered as unlikely or unclassifiable or unassessable.

Results

There were 60 olmesartan-induced enteropathy cases identified by the clinical expert (Table 4; Figure Set 1). Using the WHO criteria, 90% of cases were assessed as certain or probably related to olmesartan. The WHO causality assessment was determined as certain for 24 of the 60 cases and probable for 30 of the 60 cases. There was only one case where comorbidities were thought to possibly contribute (DSU-2012-02939) and one case where concomitant medications were thought to contribute (DSU-2012-07932). Three additional cases had another

suspect medication listed on the MedWatch form (DSM-2012-00455; DSU-2010-03745; DSU-2012-07482). Allergies were not thought to contribute for any case.

The majority of cases were elderly and female, 73.3% of cases were diagnosed at age 60 or greater and 65.0% of cases were female. A majority of cases were reported from the United States (53.3%) and Europe (31.7%). The duration of use results showed a greater range than the Mayo clinic case series.[Rubio-Tapia 2012] The 60 cases were distributed between less than 1 year (28.3%), 1 to 2 years (20.0%) and 2 to 5 years (26.7%) duration of use, with 8.3% who used the product for more than 5 years prior to symptom onset, and 16.7% with missing information on duration.

The first of the identified cases was submitted by the manufacturer to the FDA in 2004 (MFR#SU-2004-002638). The WHO assessment of causality was Probable. All eight cases received between 2004 and 2006 were assessed as Probable or Certain using the WHO criteria. In 2008, all cases had a positive dechallenge and rechallenge. Thirteen of 14 cases in 2009 had a positive rechallenge. As of 2011, the year prior to the Mayo clinic case series, the manufacturer had received reports from 46 cases with rechallenge as assessed by the clinical expert.

Older onset celiac disease cases. By the end of 2006 the manufacturer had received reports regarding two cases of patients older than 70 years old who were hospitalized and had positive dechallenge and rechallenge (SP-2006-003299; SU-2006-005596). The age of the patients is significant because celiac disease is usually, but not always, diagnosed in individuals under 65 years old.[Rashtak 2009] The positive dechallenge and rechallenge information for celiac disease in two individuals in this age group may have warranted a second look by the manufacturer given the FDA's April 2005 Guidance for Industry on E2E Pharmacovigilance Planning (developed as part of the International Conference on Harmonisation [ICH] process [ICH 2004][U.S. Department of Health and Human Services 2005]) which recommended that the manufacturer take into consideration populations not studied in the pre-approval period to predict the safety of the product after approval. The elderly are one of the populations recommended for particular consideration by this Guidance for Industry.[U.S. Department of Health and Human Services 2005] Overall 45% of the cases were 70 years or older.

Conclusions

Causality based on temporality. Only cases with a temporal relationship were included.

Causality based on dechallenge and rechallenge: All cases had a positive rechallenge by inclusion.

Causality based on WHO criteria: The majority of cases were causally related to olmesartan including 90% of the clinical expert identified olmesartan-induced enteropathy cases.

Consistency: The experiences of the cases were similar to those cases reported in the literature.

Specificity: Based on the information from the MedWatch forms, there is support of a specific relationship between olmesartan and enteropathy because comorbidities or concomitant medications were thought to play a role in only four of 60 cases.

Biologic gradient: There is no evidence of a dose response or duration of use relationship.

Experiment: All cases had a positive rechallenge by inclusion.

Objective 2. Review of the Association between Olmesartan and the Adverse Events Reported to FAERS.

Methods

Effect estimates based on the EBGM (EB05 – EB95) and PRR were calculated to assess the relative reporting ratio of symptoms associated with enteropathy with olmesartan versus the other drugs in its class. The EBGM and PRR use information from reports for all other medications in FAERS to make these calculations.[Andrews 2014] Based on the manufacturer's internal documents, they used the PRR for their disproportionality analyses. In the setting of very small observed or expected drug-outcome reports, the FDA recommends the EBGM (EB05 – EB95) over the PRR.[U.S. FDA 2015]

The EBGM calculation is conceptually similar to that of the PRR, but incorporates Bayesian "shrinkage" and stratification to produce disproportionality scores toward the null, especially when there are limited data and small numbers of cases. One important difference between the PRR and EBGM estimates is that in the case of PRR the adverse events from the product in question do not contribute to the number of "expected" cases, while all adverse events from the product contribute to the expectation when using EBGM. The statistical modifications used in the EBGM methodology diminish the effect of spuriously high PRR values, thus reducing the number of false-positive safety signals. Thus, EBGM values provide a more stable estimate of the relative reporting rate of an event for a particular product relative to all other events and products in the database being analyzed. Lower and upper 90% confidence limits for the EBGM values are denoted EB05 and EB95, respectively.

A series of event definitions were created to assess the relationship between olmesartan-containing products and gastrointestinal symptoms associated with olmesartan-induced enteropathy (Table 5). Annual and cumulative EBGM (EB05 – EB95) and PRR were calculated for each event definition. The cumulative effect estimates were calculated starting in 2002 when the first olmesartan-containing product was approved. For the calculation of the PRR, the drug of interest was included in the comparator set. Configuration AERS+SRS (S) was used for consistency with a report in which the manufacturer performed an internal calculation. Results using (S+C) were consistent to (S) (data not shown). By creating custom terms, all olmesartan-containing products were grouped as one category and compared with all ARBs other than olmesartan. Event definitions were defined using custom terms:

- 1) All celiac disease (based on preferred term) including Seriousness Yes, No and Unknown
- 2) Serious cases of celiac
- 3) Serious cases of diarrhea associated with weight loss or dehydration
- 4) Serious cases of diarrhea associated with weight loss or dehydration and a positive rechallenge

The information was tabulated and plotted. In the plots a line was placed at 2 to indicate an often-used threshold for examining a potential signal using the EB05. [Levine 2006] However, some have argued that for serious side effects, an $EB05 > 1$ should be considered.[Levine 2006] Based on the manufacturer's internal documents, they used the PRR for their disproportionality analyses. Using the PRR, a signal is defined as $PRR > 2$, at least 3 events and a chi-squared value greater than 4.[Evans 2001] I then examined if the signals were specific to olmesartan or if a signal existed for the other ARBs.

Results

PRR. The four different event definitions produced consistent evidence of signals specific to olmesartan-containing products based on the PRR (Figures 2 – 5; Tables 6 – 9). There was no signal for the other ARBs. The signal could be identified as early as 2005 (all cases of celiac disease: $n=3$, $PRR=9.85$, $\text{chi-square}=15.9$), in 2006 (serious cases of celiac disease: $n=3$, $PRR=10.5$, $\text{chi-square}=17.1$; serious cases of diarrhea with concomitant weight loss or dehydration and positive rechallenge: $n=3$, $PRR=28.2$, $\text{chi-square}=53.9$) or as late as 2007 (serious cases of diarrhea with concomitant weight loss or dehydration [no rechallenge requirement]: $n=17$, $PRR=2.39$, $\text{chi-square}=12.4$).

EB05. The results using $EB05>2$ as the threshold for a signal suggested later dates of signal detection compared with the PRR. However, using $EB05>1$ for the serious events produced signals consistent with the PRR. For all cases of celiac disease the signal was in 2006 ($PRR=2.04$). For serious celiac the signal was in 2008 using $EB05>2$ (3.01) or 2006 using $EB05>1$ (1.1). Then serious diarrhea with rechallenge signal occurred in 2007 ($EB05=3.06$) or 2006 ($EB05=1.26$). The diarrhea definition without rechallenge had signals in 2009 ($EB05=2.21$) or 2007 ($EB05=1.4$).

When olmesartan was compared with all other ARBs (except olmesartan), the signals were consistent with those described above (Appendix).

Conclusions

Causality based on temporality. Only cases with a temporal relationship were included.

Consistency: The signals are consistent with the causal associations observed in the case reports and the relationship of olmesartan with enteropathy observed in the French epidemiology study.[Basson 2016]

Strength: There was consistent evidence of an elevated PRR for all outcome definitions. The PRR was dramatically larger than 2 at the first signal for celiac disease. The PRR increased over time for celiac and the constellation of symptoms associated with chronic diarrhea.

Specificity: The signal was specific to olmesartan. A signal was not observed for the other ARBs.

Objective 3. Systematic Review of the Published Literature.

A systematic review was conducted including all levels of evidence from case reports published in the literature, non-randomized studies of the specific adverse events, and randomized clinical trials including information from ClinicalTrials.gov and manufacturer clinical trial reports.

Methods

Literature search. PubMed and Embase were searched through November 27, 2016. In order to capture all names used for olmesartan throughout the world I searched Micromedex/Martindale. [Micromedex] I searched without restriction for any other factor other than the medication name in order to have the broadest search possible. The final search in PubMed yielded 1,823 articles.

benicar OR azor or TRIBENZOR or CS-866 or RNH-6270 or Alea OR Amelior OR Azor OR Azoren OR Belfor OR Belsar OR Forzaten OR Ixia OR Olmec OR Olmesartan OR Olmetec OR Oxap OR Rezaltas OR Sartan OR Sevkar OR Votum

The same search in Embase yielded 4,452 articles. The total number of articles screened at the title/abstract level was 5,103 articles. Any article that mentioned an ARB including editorials, reviews and practice guidelines was included. All studies that did not include humans (*i.e.*, animal studies, cell lines, spectrophotometry) were excluded. Based on these criteria, 1,891 full-text articles were screened. During the full-text review the exclusion reasons were: Systematic review or meta-analysis of olmesartan, other -sartans or anti-hypertensives; No patients included; Non-systematic synthesis: Not a systematic review or guideline related to the topic (select this for notifications of drug approval); Guideline; Cost analysis/modeling that doesn't include clinical trial data; No drug of interest (olmesartan); Non-USA guideline; No outcome of interest AND not an RCT AND not a phase IV/post-marketing study; Editorial. Information from non-English articles was not included. Of the eligible studies, I categorized the information abstracted based on the study design. Guidelines, meta-analyses and pooled analyses were used to confirm that I captured all of the relevant studies in our search. Depending on the study design, different information was abstracted and assessed.

Case reports. All case reports and case series (*i.e.*, studies that included exclusively patients with olmesartan-induced enteropathy or its symptoms) were assessed. The FDA considers evidence of dechallenge and, separately, rechallenge as evidence for causality. [U.S. FDA 2005] Literature case reports will be assessed for causality. These case reports will not be used to calculate rates or estimates of the relationship between olmesartan and enteropathy. Reporting bias changes effect estimates of rates or comparative relationships. Reporting bias does not impact causal assessment of individual cases. These published case reports can contribute meaningfully to causal assessments.

Randomized Trials. All studies that randomized at least 2 groups of patients or the same patients in a cross-over design were included if at least 1 group received an olmesartan-containing product as part of the randomization protocol. No restriction was made to the duration of the study. First, I assessed which trials assessed any adverse event and then which captured gastrointestinal adverse events. For trials that captured gastrointestinal adverse events, I abstracted the information. Similarly, I assessed if gastrointestinal adverse events contributed to reasons for withdrawal. The role of the manufacturer in providing financial, material or intellectual (*i.e.*, one of the authors was an employee of the manufacturer) support was abstracted. Meta-analyses of gastrointestinal adverse events of interest including diarrhea, weight loss, dehydration and celiac disease were planned assuming at least 3 trials of similar design including medications compared, indication, patient population, follow-up and adverse events reports were homogeneous. No meta-analyses were conducted because too few published studies reported on the events of interest to allow meta-analyses of similar studies, and the majority of the published trials did not report on adverse events at all (*i.e.*, there was a potential for reporting bias). Clinical trial protocols, reports, annual reports, and other internal documents from the manufacturer were reviewed. To identify potential cases of olmesartan-induced enteropathy from these reports, I searched for the following phrases: "gastro", "diarr", "malab", "coel", "cellac", "dehyd", "vomit" and "weight".

Non-randomized studies. All prospective, retrospective, case-control or other comparative studies were included. I captured similar information for the non-randomized studies as the randomized studies. However, the non-randomized studies are more susceptible to confounding. Confounding factors are factors associated with the exposure, independently associated with the outcome and are not an intermediate between the exposure and outcome. For the studies that reported on events of interest, I performed assessments focused primarily on their control of confounding factors. Studies that did not account for confounding were discounted dramatically given the lack of specificity of the adverse event outcomes under

examination. Studies that accounted for factors such as age, sex, comorbidities and sufficient wash-out periods to observe new users and new diagnoses of olmesartan-induced enteropathy and its symptoms were considered reliable sources of information and described in detail. Similar to the randomized trials, I did not observe a sufficient number of homogenous studies to warrant meta-analyses.

ClinicalTrials.gov was searched for olmesartan-containing products by searching for the phrase "olmesartan". Alternative searches (*i.e.*, CS-866 or brand names) did not yield additional results. The outcome terms on the most recent profile were search for phrases related to gastrointestinal adverse events. The terms searched for were: gastro, intest, celiac/coeliac, diarr, dehyd, vomit, abdom, enteropathy, sprue and malab. Any specific assessment of adverse events was searched in the outcome terms using: adverse and safety.

Results

Case reports. There were 179 cases of olmesartan-induced enteropathy (Table 10). Although I searched all case reports for symptoms associated with olmesartan-induced enteropathy prior to the Mayo clinic case series [Rubio-Tapia 2012] I did not find any events that met the criteria until after the publication of that series. There were a large number of patients over age 70 affected. Similar to the MedWatch case reports, there were cases who experienced symptoms after less than 6 months of olmesartan use. Every case reported met the criteria for temporality with olmesartan use preceding the adverse event. A total of 162 cases had a positive dechallenge suggesting a WHO causality assessment of probable for the majority of cases (temporality + dechallenge). [Rubio-Tapia 2012][Talbot 2012][deFonska 2012][Dreifuss 2013][DeGaetani 2013][Nielsen 2013][Nunge 2013][Stanich 2013][Tran 2014][Théophile 2014][Tellez 2014][Florucci 2014][Khan 2014][Abdelghany 2014][Van Beurden 2014][Ianiro 2014][Hartranft 2014][Agudo 2014][Gallivan 2014][Aderinto 2014][Marthey 2014][Bhat 2014][Gaur 2014][Ulla-Rocha 2014][Santos-Antunes 2015][Heersaing 2015][Schiller 2015][Sciatom 2015][Fukushima 2015][Schlepatti 2015][Kulaj 2015][Imperatore 2016][Naik 2015][Candido 2015][Fabian 2015][Esteve 2016][Hammoudi 2016][Desruisseaux 2016][Ould 2016][NAFLD Study Group 2016][Famularo 2016][Gonzalez 2016][Machado 2016][Martins 2016]. A large number of cases had endoscopically confirmed enteropathy and information on gluten challenge (with no response to a gluten-free diet). There were eight cases with insufficient information to make a causality assessment [Prasa May 2013][DeGaetani 2013][Nguyen 2014][Cartee 2014][Martillo 2015][Ma 2015]. Overall, the vast majority of cases had evidence of dechallenge and were causally associated with olmesartan. Evidence of positive dechallenge is considered by the FDA to suggest a causal relationship between the use of a product and the adverse event. [U.S. FDA 2005] The large number of cases provides evidence of the strength of this association. Olmesartan-induced enteropathy is not an isolated event but it has impacted over 100 patients after the publication of the Mayo clinic case series in 2012.

Conclusions from case reports:

Causality based on temporality. Only cases with a temporal relationship were included.

Causality based on dechallenge and rechallenge: Nearly 80% had documented dechallenge. A small number had documented rechallenge.

Causality based on WHO criteria: The majority of cases were causally related to olmesartan based on dechallenge information and objective evidence of enteropathy.

Consistency: The experiences of the cases were similar to those cases reported in the MedWatch forms. The major difference is that the literature cases were less likely to have rechallenge information. As described in Strom's *Pharmacoepidemiology*, "This type of challenge - re-challenge situation is relatively uncommon, however, as physicians generally will avoid exposing a patient to a drug if the patient experienced an adverse reaction to it in the past."

Experiment: The majority of cases had a positive dechallenge.

Randomized Trials. The manufacturer performed 191 clinical trials associated with olmesartan. [Wang 2016] I identified 227 publications associated with randomized trials in the literature search (Tables 11-13). Some trials were associated with multiple publications including COACH, COLM, ORIENT, OSCAR, ROADMAP and TRINITY. The indication for the majority of the trials was hypertension, although ROADMAP and ORIENT included patients with type 2 diabetes to prevent microalbuminuria and diabetic nephropathy. The majority of trials were shorter than 1 year. Over 20 trials were one year or longer (ROADMAP, ANTIPAF, DEAR, OLAS, AORTA II, MORE, OCTOPUS, OSCAR, COLM, OLIVUS, ORIENT, TRINITY, SUPPORT) [Haller 2011][Kihouchi 2011][Goette 2012][Fogari 2008][Miyashita 2009][Derosa 2010][Nakamura 2010][Tsutamoto 2010][Aoki 2015][Martinez-Martin 2011][Smith 2006][Takami 2013][Stumpe 2007][Hidaka 2007][Iseki 2009][Ogawa 2012][Ogihara 2014][Hirohata 2012][Imai 2006][Kereiakes 2012][Rosendorff 2009][Mourad 2009][Schmieder 2011][Laurent 2014][Sica 2014][Kreutz 2014][Hidaka 2011][Sakata 2015]. Trials tended to have more male (>50%) than female participants with a wide range from no included females [Kreutz 2006] to exclusively females [Luis 2010]. The oldest mean age of trial participants was in the early 70s and the youngest were healthy subjects that contributed to pharmacokinetic studies.

The majority of the publications did not report on gastrointestinal adverse events (79%; 182/230). Of those that did report, many did not specify what threshold or definitions of adverse events that they planned to report and there was inconsistency between publications on this threshold (i.e., ROADMAP: "at least 3% of the patients in either study group" [Haller 2011] vs. ROADMAP: "Treatment emergent adverse events" [Menne 2012]). When adverse events were reported they were often referred to as treatment emergent adverse events. [Kereiakes 2007] [Barrios 2009] [Fogari 2010] [Fogari 2010a] [Hazan 2010]. These adverse events were defined as "A treatment-emergent adverse event (TEAE) was defined as an adverse event with an onset on or after day 1 through to the end of the study or, if reported during pre-randomization, an adverse event that increased in severity from day 1 through to the end of the study". [Kereiakes 2007] Other definitions of adverse events included more than 1% of the treatment population [Weir 2011] [Neutel 2001] [Volpe 2009] and at least one dose of the trial medication. [Mallion 2007][Zhu 2014]. Definitions used in a single study were serious adverse events reported in more than 10 patients in each group [Saruta 2015] and more than 6% of patients. [Rosendorff 2009]. There were no clinically meaningful differences in gastrointestinal symptoms between groups. No cases of celiac disease or enteropathy were reported in the trial publications.

Conclusions from randomized trials. The absence of reported cases of celiac disease from the published trials and clinical trial reports does not provide evidence that there is no causal relationship between olmesartan-containing products and olmesartan-induced enteropathy. There were limitations in the design of the trials and the total number of participants observed (as described below). The limitations in the trial design prevented the investigation needed to identify a disease defined by more than one presenting symptom.

Based on information available after the identification of olmesartan-induced enteropathy independent of the manufacturer, I identified a case of olmesartan-induced enteropathy that was diagnosed during one of the largest and longest duration olmesartan trials, ROADMAP. The event rate based on this one case in ROADMAP exceeds the event rate observed in the French epidemiology study and Mini-Sentinel. FDA specifically recognizes the importance of post-marketing information to identify safety concerns [U.S. FDA 2005]:

Risk assessment during product development should be conducted in a thorough and rigorous manner; however, it is impossible to identify all safety concerns during clinical trials. Once a product is marketed, there is generally a large increase in the number of patients exposed, including those with co-morbid conditions and those being treated with concomitant medical products. Therefore, postmarketing safety data collection and risk assessment based on observational data are critical for evaluating and characterizing a product's risk profile and for making informed decisions on risk minimization.

Causality based on temporality. The case identified in ROADMAP was hospitalized for enteropathy after the start of the trial.

Consistency: Only one definitive case was identified in a randomized trial. However, the trials were not designed in a way to capture conditions defined by a constellation of symptoms that may not be identical for all patients.

Strength. The event rate based on this one case in ROADMAP exceeds the event rate observed in the French epidemiology study and Mini-Sentinel.

Biologic gradient Dose response could not be assessed as only one case was identified definitively.

Experiment: The randomized trials did not collect information related to olmesartan-induced enteropathy.

Non-randomized studies.

Consistent with the finding from the randomized studies, the majority of the 194 non-randomized studies did not report adverse events in their publications (Tables 11-12). Most studies were between 1 month and 1 year duration among the retrospective and prospective studies.

Fourteen articles reported on gastrointestinal adverse events from prospective studies (Table 14). The adverse events were reported by group but no analysis was performed to calculate an effect estimate taking into account potential confounding factors.

Five retrospective studies reported on gastrointestinal adverse events (Table 15). The details of each study and their results are described separately.

United States 2005-2010, younger individuals with diabetes. Padwal used a database of commercially insured (traditionally aged less than 65; mean age was 54.3) individuals in the United States (Optum) to examine pharmacy, inpatient, outpatient and laboratory encounters between 2005 and 2010.[Padwal 2014] Events in 2004 were used to determine exclusion criteria (no cellac or ARB use during that year). Individuals who switched from olmesartan to another ARB were excluded. An alternative approach (and the correct approach for time to

event analysis) is to end followup at the time the individual switched drugs or to reclassify the individual to the new exposure group at the time of drug switching taking into account any carryover effects. Another appropriate technique is to apply this exclusion criteria to all ARBs (exclude all individuals who switched). A subgroup analysis performed this correct method of handling censoring but did not report the results for the gastrointestinal events. The authors examined time from new ARB initiation to hospitalization or death among individuals with diabetes and compared olmesartan to the other ARBs. A subanalysis was performed to examine time to hospitalization for a gastrointestinal condition and time to hospitalization for colitis. The study sufficiently adjusted for confounding. The authors did not find a statistically significant difference between olmesartan and the other ARBs for death, all-cause hospitalizations, gastrointestinal hospitalizations or colitis-associated hospitalizations. This study did not study the symptoms associated with the hospitalization. Due to the lack of specificity of the symptoms of olmesartan-induced enteropathy and the lack of examination of celiac disease, malabsorption or composite symptoms associated with enteropathy, this study does not contribute to the evidence.

United States 2007-2010, Medicare population.[Graham 2014] This study aimed to examine rates of cardiovascular hospitalizations and deaths subsequent to the findings in ROADMAP related to cardiovascular disease. Graham used a new user criteria of 6 months without an ARB instead of 1 year as in Padwal. No specific analysis of gastrointestinal events was performed. The authors did state that hospitalizations for gastrointestinal disorders were common (9.4%) but separate results by olmesartan versus other ARB user were not provided. Adjusted analyses were not performed. Due to the lack of analyses on events of interest, this study does not contribute to the evidence.

United States 2007-2013, Columbia University Medical Center, Case-control.[Graywood 2014] The authors compared the indication for gastrointestinal endoscopy combined with medication use to examine the relationship between olmesartan and diarrhea. Only 105 total users of olmesartan were identified. Medication use was not validated by chart review or by verifying prescription history. Models were adjusted for age and sex but not comorbidities. Individuals with and without hypertension and diabetes were included and no adjustments were made for these comorbidities. Individuals who underwent endoscopy for diarrhea were more likely (but not statistically significantly) to have reported olmesartan use than controls undergoing endoscopy for reflux (OR 1.99; 95% CI 0.79-5.00). However, due to the small number of olmesartan users and the failure to account for confounding by comorbidities or other medications in the analyses, this study does not contribute to the evidence.

United States, Columbia University Medical Center, Case-control.[Lagana 2015] The study design from the previously reported publication at this center was modified to identify patients undergoing endoscopy who had an indication for abdominal pain and documented olmesartan use (n=20). They were compared with 20 age and sex matched individuals undergoing endoscopy for abdominal pain without a record of olmesartan use. The identification and matching was then performed for 20 individuals with use of another ARB. Pathology specimens were reviewed for all individuals to identify factors associated with olmesartan-induced enteropathy. Although there was no statistically significant finding between cases and controls, the authors noticed a trend for "architectural distortion (villous atrophy and/or crypt hyperplasia), generalized increase in intraepithelial lymphocytosis (IEL) and chronic inflammation." Villous atrophy was present in 25% of evaluated olmesartan users compared with 6-11% of the other groups. The authors suggest that there may be a spectrum of symptoms or a progression of symptoms associated with olmesartan-induced enteropathy. Because the indication for endoscopic procedure was abdominal pain, and not diarrhea, the authors appear to imply that the symptoms progress from abdominal pain to diarrhea and the subsequent weight loss and potential for dehydration that comes with a more severe malabsorption disorder.

They suggest that these patients should undergo drug dechallenge for abdominal pain resolution. Due to the design limitations (primarily no adjustment for confounding), this study does not contribute to the evidence of a causal relationship between olmesartan and olmesartan-induced enteropathy. This study does raise an important hypothesis: that olmesartan-induced enteropathy can be prevented by early dechallenge for individuals with mild gastrointestinal symptoms.

France National Health Insurance claim database, 2007 – 2012, National Claims Database. This was the only population-based epidemiology study that was identified that accounted for all confounding factors and specifically aimed to study olmesartan-induced enteropathy. The characteristics of this study are listed and compared with the FDA's Mini-Sentinel analysis in Table 16. This population-based study of adults who took olmesartan, another ARB or an ACEI was compared for hospitalizations for malabsorption or celiac disease. A prescription fill after a one year period without medication use was considered a new user. Individuals with hospitalizations for malabsorption in the year prior to first utilization of an ARB or ACEI were also excluded (see Table 16 for full inclusion and exclusion criteria). The authors found that olmesartan was associated with an increased rate of hospitalization for malabsorption and celiac disease and that greater duration of use was associated with an increased relative rate as shown the tables from the manuscript (Shaded Tables 3 and 4) below. This study provides evidence of a relationship between olmesartan and malabsorption and celiac disease compared with ACEI with at least 1 year of use (adjusted RR 3.66 for 1-2 years of use and RR 10.65 for >2 years of use). In contrast, no relationship was seen between the other ARBs and malabsorption or celiac disease compared with ACEI. This finding is particularly impactful as olmesartan users contributed the least amount of person-years (Shaded Table 2 below). This is significant because the ability to observe events was lowest for olmesartan as there were fewer years of follow-up available (referred to as low statistical power, i.e., there was the greatest chance of not detecting an effect when an effect truly existed for olmesartan).

Table 3 Crude and adjusted rate ratios of hospitalisation with a discharge diagnosis of intestinal malabsorption over time (ref: ACEI)

	Crude rate ratio	95% CI	p Value	Adjusted rate ratio	95% CI	p Value
Overall population						
Olmesartan	2.34	(1.64 to 3.32)	<0.0001	2.49	(1.73 to 3.57)	<0.0001
Other ARBs	0.77	(0.57 to 1.04)	0.09	0.78	(0.58 to 1.07)	0.12
Treatment duration <1 year						
Olmesartan	0.71	(0.36 to 1.39)	0.32	0.76	(0.39 to 1.49)	0.43
Other ARBs	0.57	(0.37 to 0.86)	0.007	0.58	(0.38 to 0.88)	0.01
Treatment duration 1–2 years						
Olmesartan	3.44	(1.73 to 6.82)	0.0004	3.66	(1.84 to 7.29)	<0.001
Other ARBs	1.02	(0.55 to 1.89)	0.95	1.03	(0.56 to 1.92)	0.92
Treatment duration >2 years						
Olmesartan	10.09	(4.80 to 21.20)	<0.0001	10.65	(5.05 to 22.46)	<0.0001
Other ARBs	1.66	(0.80 to 3.48)	0.18	1.68	(0.80 to 3.51)	0.18

ACEI, ACE inhibitor; ARB, angiotensin receptor blocker.

Table 4 Adjusted rate ratios of hospitalisation with a discharge diagnosis of coeliac disease (ref: ACEI)

	Adjusted rate ratio	95% CI	p Value
Overall population			
Olmesartan	4.39	(2.77 to 6.96)	<0.0001
Other ARBs	0.91	(0.58 to 1.42)	0.68
Treatment duration <1 year			
Olmesartan	1.98	(0.85 to 4.61)	0.11
Other ARBs	1.07	(0.56 to 2.05)	0.84
Treatment duration 1–2 years			
Olmesartan	4.36	(2.04 to 9.34)	<0.001
Other ARBs	0.77	(0.36 to 1.67)	0.51
Treatment duration >2 years			
Olmesartan	10.21	(4.21 to 24.76)	<0.0001
Other ARBs	0.94	(0.36 to 2.47)	0.90

ACEI, ACE inhibitor; ARB, angiotensin receptor blocker.

Table 2 Risk over time: descriptive data

	ACEI	Olmesartan	ARB
PY	3 646 311	860 894	4 503 098
0–1 year	1 584 921	377 748	1 706 722
1–2 years	922 124	223 477	1 153 054
≥2 years	1 139 266	259 668	1 643 322
Number of events	87	48	83
0–1 year	59	10	36
1–2 years	18	15	23
≥2 years	10	23	24
Crude incidence rate (per 100 000 PY)	2.39	5.58	1.84
0–1 year	3.72	2.65	2.11
1–2 years	1.95	6.71	1.99
≥2 years	0.88	8.86	1.46

ACEI, ACE inhibitor; ARB, angiotensin receptor blocker; PY, person-years.

Conclusions from the non-randomized studies. The majority of the prospective non-randomized studies did not report on gastrointestinal side effects. Of the five eligible retrospective studies that reported on gastrointestinal events, only one study estimated the rate of olmesartan-

Induced enteropathy and calculated a comparative estimate of the symptoms of olmesartan-induced enteropathy among users of olmesartan compared with another anti-hypertensive (ACEI) adequately accounting for confounding.[Basson 2016] This study also compared events in other ARBs versus ACEIs. Only olmesartan was associated with malabsorption and celiac disease, and increasing duration of use was associated with increased relative rates of malabsorption and celiac disease.

Causality based on temporality: The participants with enteropathy developed symptoms after taking olmesartan.

Consistency: The French epidemiology study identified a strong relationship between olmesartan and enteropathy. A strong relationship is consistent with the other sources of evidence.

Strength. The rate of hospitalization for malabsorption and celiac disease is 10 times greater with at least 2 years duration of olmesartan use compared with ACEI use in the French epidemiology study. This finding is statistically significant. Based on my experience as an epidemiologist it is rare to encounter this magnitude of a statistically significant finding.

Biologic gradient Dose response could not be assessed. The French epidemiology study did not test for dose-response.

ClinicalTrials.gov Results The search yielded 123 studies of which 48 (39%) had sponsorship at least in part from the manufacturer (Table 17). No study specifically mentioned a gastrointestinal event in the outcomes list. A total of 29 studies mentioned the collection of adverse events or safety in general in their outcomes list, and 8 (28%) of these included sponsorship from the manufacturer. Despite the clear signals of an association between olmesartan-containing products and enteropathy, contacts by the FDA to assess the relationship between olmesartan and celiac disease and an FDA Safety Communication, not a single trial or post-marking study has been designed to assess gastrointestinal events according to the publicly posted trial information on ClinicalTrials.gov.

Evidence to support my conclusion that the randomized trials do not provide support for an absence of a causal relationship between olmesartan and enteropathy. The absence of reported cases of celiac disease from the published trials does not provide evidence that there is no causal relationship between olmesartan-containing products and olmesartan-induced enteropathy. Causal relationships of no effect are difficult to establish, particularly for relatively rare events like enteropathy. A trial must be designed to follow a sufficient number of individuals such that if a difference in event rates is not observed, it is unlikely that the lack of difference is due to chance. When thinking of efficacy studies, the type I error is the probability of rejecting the null hypothesis (that the drug has no effect) if it is in fact true. Alpha=0.05 is standard. Type II error is the probability of accepting the null hypothesis (and thus failing to use the new treatment) when in fact it is false (the treatment works). By fixing, in advance, the rates of type I and type II error, the number of mistakes made over many different experiments would be limited. When designing a clinical trial, calculations are made to ensure that the study is large enough to keep both type I and type II error rates small.[Sterne 2001]

Table from BMJ. 2001 Jan 27; 322(7280): 226-231; Possible errors in interpretation of experiments, according to the Neyman-Pearson approach to hypothesis testing. Error rates are proportion of times that type I and type II errors occur in the long run.

Result of experiment	The truth	
	Null hypothesis true (treatment doesn't work)	Null hypothesis false (treatment works)
Reject null hypothesis	Type I error rate (α)	Power = 1 - type II error rate
Accept null hypothesis		Type II error rate

The longest duration trial performed by the manufacturer was ROADMAP.[Haller 2011] I will focus on the design characteristics of this trial because, of the placebo-controlled randomized trials performed, it has the highest power given its large size and long duration. All other studies with smaller Ns and shorter durations have even less power. According to the supplementary file of the NEJM trial publication, the trial was designed to detect a 30% difference between treatment groups (based on an unspecified event rate in the control population) with 90% power and 5% significance level ($=\alpha$).[Haller 2011] A clinical study report associated with ROADMAP provided greater detail:

9.7.2. Determination of Sample Size

It was planned that a total of 4400 patients would be randomised in the study. The sample size was based on estimated yearly average incidence rates of microalbuminuria of 2% in the placebo group yielding 90.39% of event-free patients after a median time of 5 years of treatment.⁴⁵ Based on the log-rank test and assuming a hazard ratio of 1.433 (ie, a 30% risk reduction by olmesartan medoxomil therapy), comparing times to event with 90% power on the 4.9% significance level was calculated to require a minimum of 2033 patients for the full analysis set of each of the



Daichi Sankyo

Clinical Study Report: SE-866/44
Version: Final 1.0, 14 Jun 2010

2 treatment arms (ie, it was expected that 326 events of microalbuminuria would be observed). To compensate for withdrawals for reasons other than microalbuminuria, 2200 randomised patients per treatment arm were planned.

I attempted to calculate the sample size required to observe a difference in enteropathy between groups using a log-rank test as was done for the primary outcome of the ROADMAP study (Stata calculation: `stpower logrank .9039, hratio(0.6978) power(.9) alpha(0.049)`). I based the rate on 1) the rate of malabsorption in the unexposed group as observed in the French epidemiology study among users of ACEIs and ARBs other than olmesartan (2.39 and 1.84 per 100,000 person-years) and 2) general population's celiac disease annual incidence rate (1.3 per 100,000 in 1999 to 6.5 per 100,000).[Riddle 2012] The rates in the unexposed populations of Mini-Sentinel were similar or lower to those in the French epidemiology study. The prevalence of celiac disease in the population with type 2 diabetes is thought to be the same as the general population.[Kylökäs 2016] I chose to use the incidence rates for celiac disease because the Mayo Clinic case series[Rubio-Tapia 2012] and the FDA request for more information were based on the identified association between olmesartan and celiac-like symptoms.

Because the rates were so small, I was unable to calculate the estimated sample size with a log-rank test using standard software (stpower logrank .000192, hratio(2) power(.8) alpha(0.05); "survival probability is too small ($\leq 1.0e-6$)). Thus, I used tests of proportions (sampsi .000192 .00192, power (0.8) alpha (0.05). Based on these assumptions of the underlying rate, alpha=0.05 and a range of large effect estimates as observed in the French epidemiology study, the number of participants randomized and analyzed per group to make an inference with 80% power was very large. The ROADMAP trial included 4,449 randomized patients (2 of whom never took treatment in the randomized period). [Haller 2011] Because 4,449 is smaller than all numbers in the table, the study was not sufficiently powered to detect any of the relative differences given the assumed prevalence among the placebo group.

Number of participants required per study group to observe relative rate increases of 2-10*

Assumed proportion in OLM unexposed	Relative Rate				
	RR 2	RR 4	RR 6	RR 8	RR 10
Celiac lower limit 0.000032 (3.2*1/100k)	797071	156393	80685	53601	39945
French ARB 0.00005888 (3.2*1.84/100k)	433174	84991	43847	29127	21706
French ACEI 0.00007648 (3.2*2.39/100k)	333482	115315	33755	22423	16710
Celiac upper limit .000192 (3.2*6/100k)	44475	65430	33755	22441	6652

*alpha=0.05 (2-sided); power=80% Unexposed estimate based on the French epidemiology study rates and a range of estimates for celiac disease in the general population (ranging from annual incidence of 1-6/100,000 population) with upper estimates multiplied by 3.2 for a 3.2-year study.

Despite ROADMAP being underpowered, a case of olmesartan-induced enteropathy was identified among the study subjects by the clinical expert. The manufacturer received this case in 2006 (Study: SE-866/44, Patient no. 1630007, Random no. 4790, Centre no. 1630). In the MedWatch form generated by the manufacturer there is clear evidence of a positive dechallenge and rechallenge (MFR#SP-2006-003369). Using this case to calculate a rate of olmesartan-induced enteropathy from ROADMAP, the event rate is even higher than the unadjusted rate from the French epidemiology study among users of olmesartan for greater than 2 years (8.86/100,000 person-years). The unadjusted rate from ROADMAP is 14.09/100,000 person-years.

Unfortunately, this ROADMAP olmesartan-induced enteropathy case was misidentified as a case of gastroenteritis during the trial (Table 12.9 of Protocol dated 14 Jun 2010 (OLM-DSI-0001802066 ROADMAP CLINICAL STUDY REPORT SE-86644) and on the MedWatch form (OLM-DSI-0004767148_SP-2006-003369 ROADMAP MFR# SP-2006-003369). Although the investigator could have broken the code to identify if this serious case had received olmesartan, there is not evidence that this unblinding occurred.

9.5.3.18.2. Procedure for the Investigator

In case of an occurrence of a SAE, the investigator was obliged:

- To ensure appropriate medical treatment, to decide whether to withdraw the patient and whether to break the randomisation code.
- To consider whether a blood sample for drug assay was to be taken (if appropriate this should be discussed with the monitor).
- To notify the monitor or the person(s) named in the protocol immediately (or contact the person responsible for Drug Safety at Daiichi Sankyo Europe GmbH) by telephone of the occurrence of the SAE. The information was to include the name of the investigator, centre number, study identification, study patient identification, investigational drug, and suspected AE term.

There were 14 patients who had their code broken during the study: 5 patients had microalbuminuria that led to the investigator unblinding the patient (patient numbers 440205, 440467, 441227, 443979, 445660), 6 patients had an AE leading to unblinding (patient numbers 442206, 442400, 443139, 443396, 444454, and 445227), 2 patients withdrew consent (patient numbers 441977 and 444596) and 1 patient died (patient number 442887).

After the Mayo Clinic case series was published and after the completion of the trial, a study investigator did not identify this positive rechallenge case as a case of olmesartan-induced enteropathy. A letter to the editor co-authored by Haller in response to the Mayo Clinic case series concludes with "We cannot rule out the possibility that in this very rare disease the intestinal renin-angiotensin system plays a role; however, our data from the ROADMAP database did not identify a link between olmesartan use and the occurrence of gastrointestinal disease." [Menne 2012] As stated above, the study did not follow a sufficient number of participants to rule out a link, and Haller's statement that the possibility of a causal relationship between olmesartan and enteropathy cannot be ruled out based on the design of ROADMAP is accurate.

Table 12.9: Overview of Serious TEAEs During the Double-Blind Period by Preferred Term (SAF-DB)

Serious TEAEs: Brief Summary and Preferred Terms	Olmesartan N = 2232 n (%)	Placebo N = 2215 n (%)	Total N = 4447 n (%)
Patients with at least 1 serious TEAE	335 (15.0)	337 (15.2)	672 (15.1)
Patients with at least 1 mild serious TEAE	90 (4.0)	122 (5.5)	212 (4.8)
Patients with at least 1 moderate serious TEAE	158 (7.1)	158 (7.1)	316 (7.1)
Patients with at least 1 severe serious TEAE	127 (5.7)	114 (5.1)	241 (5.4)
Patients with at least 1 drug-related serious TEAE	4 (0.2)	1 (0.0)	5 (0.1)
Serious drug-related TEAEs			
Mild			
Circulatory collapse	1 (0.0)	0 (0.0)	1 (0.0)
Hypotension	1 (0.0)	0 (0.0)	1 (0.0)
Moderate			
Gastroenteritis	1 (0.0)	0 (0.0)	1 (0.0)
Vasculitis necrotising	1 (0.0)	0 (0.0)	1 (0.0)
Severe			
Ischaemic cardiomyopathy	0 (0.0)	1 (0.0)	1 (0.0)
Hypertensive crisis	1 (0.0)	0 (0.0)	1 (0.0)

SAF-DB = safety set for the double-blind period; TEAE = treatment-emergent adverse event
Data source: Section 14; Tables 14.3.1.3.1.1, 14.3.1.3.8.1, and 14.3.1.3.15.1

5. Describe Event or Problem

Event Verbatim [PREFERRED TERM] (Related symptoms if any separated by commas)

HOSPITALISATION BECAUSE OF GASTROENTERITIS

[Gastroenteritis]

HYPOKALAEMIA [Hypokalaemia]

HYPOCALCAEMIA [Hypocalcaemia]

Case Description:

Initial information received on 05-DEC-2006:

An investigator reported that a 56 year-old Caucasian female [Redacted] weight 84 kg, height 158 cm) was hospitalized due to gastroenteritis with hypokalaemia. The subject was screened for study SE-866/44 (centre no. 1630, patient no. 1630007, random no. 4790) on 13-JAN-2006 and received 40 mg olmesartan medoxomil or placebo o.d. as active trial medication for the indication prevention of microalbuminuria since 15-FEB-2006

TABLE. Gastrointestinal TEAEs Reported in the ROADMAP Database			
Event	No. (%) of patients		P-value
	Olmesartan, 40 mg (n=2232)	Placebo (n=2215)	
Intestinal-associated TEAE	78 (3.5)	94 (4.2)	.20
Diarrhea	51 (2.3)	52 (2.3)	
Gastroenteritis	17 (0.8)	25 (1.1)	
Colitis	1	6 (0.3)	
Enteritis	2 (0.1)	4 (0.2)	
Gastroduodenitis	4 (0.1)	2 (0.1)	
Colitis, ulcerative	2 (0.1)	2 (0.1)	
Duodenitis	2 (0.1)	2 (0.1)	
Gastrointestinal disorder	3 (0.1)	1	
Gastrointestinal infection	1	3 (0.1)	
Enteritis, infectious	0	2 (0.1)	
Abdominal discomfort-associated TEAE	127 (5.7)	125 (5.6)	.95
Abdominal pain	61 (2.7)	52 (2.3)	
Upper	26 (1.2)	24 (1.1)	
Lower	2 (0.1)	1	
Location not reported by physician	33 (1.4)	27 (1.2)	
Dyspepsia	34 (1.5)	29 (1.3)	
Nausea	30 (1.3)	34 (1.5)	
Vomiting	13 (0.6)	13 (0.6)	
Flatulence	6 (0.3)	9 (0.4)	
Abdominal discomfort	4 (0.2)	4 (0.2)	
Irritable bowel syndrome	2 (0.1)	3 (0.1)	
Epigastric discomfort	2 (0.1)	2 (0.1)	
Gastrointestinal pain	1	0	
Fatigue	25 (1.1)	20 (0.9)	
Weight decrease	17 (0.8)	11 (0.5)	

ROADMAP = Randomized Olmesartan and Diabetes Microalbuminuria Prevention; TEAE = treatment-emergent adverse event.

Flaws in the design and conduct of ROADMAP. A major design flaw with ROADMAP was the way that adverse events were identified. A major flaw in the conduct of ROADMAP was the lack of evidence that the protocol was followed up for the adverse events that were identified. The limitations in the trial design and conduct prevented the investigation needed to identify a disease defined by more than one presenting symptom.

According to the Bucharest criteria, olmesartan-induced enteropathy is defined by a constellation of symptoms.[Rostami 2015] However, the failure to identify cases of enteropathy or celiac disease in the randomized trials is not surprising given the method of capturing adverse events, including instructing investigators to specifically not ask about concomitant symptoms. The method of capturing adverse events was generally similar across trials and relied on an open-ended question and response. Adverse events were collected during study visits as follows for ROADMAP (Clinical Study Report: SE-866/44 Version: Final 1.0, 14 Jun 2010):

All non-serious AEs were to be properly documented by the investigator on the AE Report Form as part of the CRF. They were to be reported to the monitor during monitoring visits. Non-serious AEs were listed as routine information included in monthly reports.

At each visit, the investigator was to ask the patient about AEs. The questions were to be asked in an open manner and no concomitant symptoms were to be insinuated [emphasis added]. The recommended standard question was as follows:

"Have you experienced any change in your health or in your general condition since the previous visit?"

The information recorded was to be based on a full clinical evaluation of the patient as appropriate and was to include general and specific questioning.

AEs were as a rule documented in the section for recording AEs in the CRF (Adverse Event Report Form). They were not to be entered as comments in other sections of the CRF. The Adverse Event Report Form had to be completed thoroughly in detail. It was also extremely important to complete the questions concerning outcome, relationship to investigational product or comparator drug, if appropriate, serious (yes/no), expected/unexpected (on SAE report forms), because this information was necessary to decide on expedited reporting to authorities. If necessary, the causality assessment could be added later by the investigator after obtaining further results. The causality assessment had to be signed and dated by the investigator. If a patient displayed the same AE at several study visits, the end date was to remain empty. The end date must be inserted after this AE had resolved.

The lack of specificity of this recommended (not required) question combined with the composite nature of the symptoms associated with olmesartan-induced enteropathy and the direction for the study investigator to NOT ask about concomitant symptoms provide evidence that it would be nearly impossible for an investigator to identify a case of olmesartan-induced enteropathy in a trial unless a patient was hospitalized and the investigator was allowed, according to the protocol to take into account the full-spectrum of symptoms.

Given the combination of symptoms required to diagnose enteropathy, the best method of assessing it would have been during the protocol required dechallenge assessment for those who left the study with adverse events or continued to experience adverse events at the end of the trial:

"All patients with unresolved AEs at the end of the study, except those who dropped out before randomisation or starting active treatment, were to be included in a safety follow-up visit in order to check response of AEs to dechallenge. The safety follow-up visit took place 1 to 2 weeks after the final examination visit."

The dechallenge results are not systematically analyzed in the clinical trial reports. In this ROADMAP trial report the dechallenge results would be of particular interest to examine the rechallenge information on the serious case of gastroenteritis (MFR# SP-2006-003369) identified by the clinical expert as a positive dechallenge/rechallenge case based on the text in the MedWatch form. This case occurred after 9 months of olmesartan 40mg use (started 15-FEB-2006, developed gastroenteritis on 01-NOV-2006 and was hospitalized on 17-NOV-2006). The dechallenge assessments of the non-serious cases of gastroenteritis in the cases and controls documented by Haller in his letter to the editor would also be useful to see if there were differences in positive dechallenge between those receiving olmesartan versus placebo. [Menne 2012]

The enteropathy case identified from ROADMAP with a positive rechallenge was not unique. Another Medwatch report from ROADMAP (not associated with a rechallenge) coded as acute prerenal failure in its preferred term had experienced intermittent diarrhea and vomiting prior to her hospitalization [DSM-2008-01071]. Had the manufacturer investigated cases with symptoms of celiac disease from their own trials in response to the rechallenge positive case reports and signals from FAERS in 2006, a causal association between olmesartan and enteropathy could have been detected.

Summary

In conclusion, it is my opinion, to a reasonable degree of scientific certainty, that there is sufficient evidence to establish a causal relationship between olmesartan and enteropathy. There is consistent evidence from the MedWatch case reports and signals from FAERS that this causal association was established in 2006.

Dr. M. H. 30 Nov 2016

Exhibit B

Protected Information - Susan Huftless, Ph.D.

1 IN THE UNITED STATES DISTRICT COURT
2 FOR THE EASTERN DISTRICT OF NEW JERSEY

3 - - -

4
5 IN RE: BENICAR : CIVIL ACTION
6 (Olmesartan) PRODUCT : :
7 LIABILITY LITIGATION : NO. 15-2606
8 : (RBK) (JS)
9 :
10 :
11 :

12 - - -

13 February 28, 2017

14 - - -

15 PROTECTED INFORMATION

16 Oral deposition of
17 SUSAN HUFTLESS, Ph.D., taken pursuant to
18 notice, was held at the law offices of
19 Venable, LLP, 750 East Pratt Street,
20 Suite 900, Baltimore, Maryland, beginning
21 at 8:36 a.m., on the above date, before
22 Michelle L. Gray, a Registered
23 Professional Reporter, Certified
24 Shorthand Reporter, Certified Realtime
 Reporter, and Notary Public.

 - - -

 GOLKOW TECHNOLOGIES, INC.
 877.370.3377 ph | 917.591.5672 fax
 deps@golkow.com

Protected Information - Susan Huftless, Ph.D.

1 APPEARANCES:

2

3

ROBINS KAPLAN, LLP

BY: TARA SUTTON, ESQUIRE

4

HOLLY H. DOLEJSI, ESQUIRE

800 LaSalle Avenue, Suite 2800

5

Minneapolis, Minnesota 55402

(612) 349-8500

6

tsutton@robinskaplan.com

hdolejsi@robinskaplan.com

7

- and -

8

LIEFF CABRASER HEIMANN & BERNSTEIN

9

BY: LEXI J. HAZAM, ESQUIRE

275 Battery Street 29th Floor

10

San Francisco, California 94111

(415) 956-1000

11

lhazam@lchb.com

Representing the Plaintiffs

12

13

VENABLE, LLP

BY: BRUCE R. PARKER, ESQUIRE

14

SHANNON E. BEAMER, ESQUIRE

750 E. Pratt Street, Suite 900

15

Baltimore, Maryland 21202

(410) 244-7534

16

brparker@venable.com

Sebeamer@venable.com

17

- and -

18

DRINKER, BIDDLE & REATH, LLP

19

BY: SUSAN SHARKO, ESQUIRE

600 Campus Drive

20

Florham Park, New Jersey 07932

(973) 549-7000

21

susan.sharko@dbb.com

Representing the Defendant, Daiichi

22

Sankyo, Inc.

23

24

Protected Information - Susan Huftless, Ph.D.

1 APPEARANCES: (Cont'd.)

2

ALSO PRESENT:

3

Amy Klug (Daiichi-Sankyo)
(Via telephone)

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1 around then.

2 Q. Describe for me what you
3 received?

4 A. I mean, I received a link to
5 go to a website to download the MedWatch
6 forms.

7 Q. Do you remember how many
8 forms that link gave you access to?

9 A. Yes.

10 Q. How many?

11 A. So there were about 300.

12 Q. What is your understanding
13 as to who collected those 300 that were
14 made available to you?

15 A. Sure. So I had been having
16 a communication with Tara and Lexi. And
17 I had been talking about with them, about
18 identifying cases --

19 MS. SUTTON: Object. You
20 can't talk about -- reveal our
21 communications.

22 THE WITNESS: Oh, I'm sorry.

23 Okay. Can you say the
24 question again? I'm sorry.

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1 BY MR. PARKER:

2 Q. What is your understanding
3 of who collected the 300 MedWatch reports
4 that were provided to you via the link?

5 A. Oh, so their staff under my
6 direction based on criteria that I had
7 requested.

8 Q. So let me make sure I
9 understand. You gave criteria, which
10 we'll get into in a moment, to
11 plaintiffs' counsel to conduct a search,
12 and that generated the 300 that you were
13 given access to?

14 A. Correct.

15 Q. And were those search
16 criteria the MedDRA terms that
17 Dr. Leffler gave you?

18 A. No. That came afterwards.

19 Q. I'm sorry. What came after?

20 A. So the -- so I -- so I was
21 reviewing the literature and was coming
22 up with a list of criteria and was
23 thinking of the symptoms that were
24 associated with olmesartan-induced

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1 enteropathy.

2 And based on those initial
3 criteria, I had requested -- I'm sorry.
4 I'm trying to remember what happened.

5 Q. Please take your time. It's
6 important.

7 A. So based on symptoms I had
8 requested, they look for -- they looked
9 for particular cases.

10 But that was around the time
11 I was -- I think it was just before then
12 I had talked about the preferred terms
13 with Dan.

14 Q. Dan Leffler?

15 A. Dan Leffler. Sorry.

16 Q. Okay.

17 A. Yeah. So the -- I'm sorry.
18 I'm having problems recalling what
19 happened.

20 So it was right around the
21 same time. He may have actually -- I
22 mean, I had a conversation with him. But
23 I think the preferred terms list, it was
24 more based on -- it was more based on our

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1 general conversation than his list of
2 preferred terms, the initial list of
3 preferred terms. He and I had many,
4 many -- not many. But we had several
5 conversations about the symptoms of this.

6 So I'm an epidemiologist.
7 I'm not a clinician. So I rely upon a
8 clinician to help -- to help come to
9 these conclusions.

10 So he and I had been talking
11 since around that time and before that
12 time about the symptoms that were
13 relevant. And then I made a request of a
14 set of symptoms based on those
15 conversations with Dan and my review of
16 the literature. And those were prepared
17 for by their -- by their staff.

18 Q. Whose staff? You said their
19 staff.

20 A. Their lawyers.

21 Q. Counsel?

22 A. Yeah, counsel. Thank you.

23 Q. So the end result of the
24 process you just described is you were

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1 provided a link which gave you access to
2 some 300 MedWatch reports?

3 MS. SUTTON: Objection to
4 form. Asked and answered.

5 You can go ahead.

6 THE WITNESS: Okay. So I --
7 yes, I was provided with MedWatch
8 forms based on a request of
9 criteria made by me, yeah.

10 BY MR. PARKER:

11 Q. What I want to make sure I'm
12 clear is, you were not given access to
13 the full set of MedWatch reports provided
14 to counsel and did your own search of
15 them; is that correct?

16 MS. SUTTON: Objection to
17 form. Foundation.

18 You can answer.

19 THE WITNESS: So my
20 understanding -- I mean, there
21 were thousands of MedWatch forms.
22 And it would be very time
23 consuming for me to go through
24 each of them, when many of them

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1 would be related to cardiovascular
2 events, for example.

3 So I had requested to
4 have -- to have forms related to
5 gastrointestinal disorders that
6 were associated with dechallenge,
7 because that's the current
8 consensus on olmesartan-induced
9 enteropathy.

10 BY MR. PARKER:

11 Q. Are you able to tell me
12 or -- and we'll mark your report, review
13 your report -- what the terms were that
14 you gave to plaintiffs' counsel to do the
15 search?

16 A. They -- I mean, they were
17 related to diarrhea, celiac disease,
18 malabsorption, and gastrointestinal
19 disorders. And there -- there were --
20 you know, their staff, counsel's staff,
21 did their best to do that, but I
22 subsetted it from there. You'll see that
23 as a product of the review that was
24 conducted with Dr. Leffler, that I ended

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1 up -- we ended up -- actually he ended up
2 coming down with a list of cases that
3 were the most specific and relevant to
4 making an assessment of causality to
5 address the causal relationship between
6 olmesartan and olmesartan-induced
7 enteropathy.

8 Q. Okay. You're a couple steps
9 ahead of me. Right now I just want to
10 talk about how and understand how the
11 information was gathered.

12 And if my understanding is
13 correct, you gave terms of diarrhea,
14 celiac disease, malabsorption, and
15 gastrointestinal disorders and asked to
16 have a search run of the thousands of
17 MedWatch reports to see what that would
18 generate?

19 MS. SUTTON: Objection to
20 form. Asked and answered.

21 BY MR. PARKER:

22 Q. Is that correct?

23 A. So the -- sorry, I'm not
24 used to the questioning like this. So

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1 there -- yes, related to dechallenge and
2 symptoms related to olmesartan-induced
3 enteropathy.

4 Q. You just added something. I
5 want to make sure I understand. When you
6 gave the clinical terms -- and I did get
7 them right, right? Diarrhea, celiac
8 disease, malabsorption and a broad term
9 of GI disorders.

10 A. So --

11 Q. Were those clinical terms?

12 A. Those are clinical terms. I
13 believe vomiting was also in that list.

14 Q. Okay. Very good. Anything
15 else in terms of clinical terms?

16 MS. SUTTON: Objection to
17 form.

18 THE WITNESS: So based on my
19 conversation with Dan, I believe
20 also fecal incontinence was
21 included at that time. It may
22 have only been included when we --
23 at a different point in time. I
24 may have included it at that time

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1 conducted the initial search that led to
2 the 300 that led to the narrowing that
3 you just described?

4 MS. SUTTON: Objection to
5 form. Asked and answered.
6 Misstates testimony.

7 THE WITNESS: Correct. So
8 this -- this -- the methods
9 section of my report states that I
10 received the MedWatch forms that
11 are included and summarized in my
12 report were the ones determined by
13 the clinical expert based on his
14 clinical experience to be cases
15 consistent with olmesartan-induced
16 enteropathy.

17 I list the criteria, the
18 constellation of symptoms that he
19 considered. That includes talking
20 to both -- about the preferred
21 terms and the text description,
22 because there were items in the
23 text description that weren't
24 included in the preferred terms,

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1 and that they were serious and
2 showed a rechallenge.

3 BY MR. PARKER:

4 Q. And you're referring to Page
5 17?

6 A. I am referring to Page 17.

7 Q. What's not stated here is
8 that -- the methods, is that I asked
9 counsel to conduct a search of the entire
10 MedWatch database using these terms that
11 generated a number of 300-something --
12 300-some-odd reports which were then
13 distilled down to the 60 by Dr. Leffler.

14 MS. SUTTON: Objection.

15 Form. Misstates testimony.

16 BY MR. PARKER:

17 Q. That's the process that you
18 just described, correct?

19 MS. SUTTON: Misstates
20 report.

21 THE WITNESS: So my report
22 includes the cases that I -- based
23 on the criteria that the clinician
24 determined as highly specific

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1 those being identified as serious events,
2 including hospitalization for
3 olmesartan-induced enteropathy and a
4 rechallenge.

5 So these list of criteria
6 are consistent with something called the
7 Bucharest criteria, which are now used as
8 one of the -- when a clinician encounters
9 a case with symptoms consistent with
10 olmesartan-induced enteropathy, this
11 Bucharest criteria is a consensus
12 document that describes how to treat
13 patients, how to -- it's a practice
14 pattern.

15 Q. We'll spend some time on the
16 so-called Bucharest criteria.

17 MS. SUTTON: Objection.

18 BY MR. PARKER:

19 Q. But so we're clear, you were
20 referring to Page 17, the first
21 paragraph, and the terms were diarrhea,
22 vomiting, or celiac disease?

23 A. That is correct.

24 Q. Okay. So we're clear, those

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1 were the three terms that Dr. Leffler
2 used to apply to the 300-some-odd
3 MedWatch reports that were provided to
4 you after you gave terms to counsel that
5 then reduced the 300 down to the 60?

6 MS. SUTTON: Objection to
7 form. Misstates testimony.

8 THE WITNESS: So the final
9 list of cases are a highly
10 specific list of cases that
11 have -- that are serious, most of
12 them requiring hospitalization,
13 that showed a rechallenge, and
14 either in the preferred terms or
15 the text have symptoms consistent
16 with olmesartan-induced
17 enteropathy that, based on
18 Dr. Leffler's clinical experience,
19 are cases of olmesartan-induced
20 enteropathy.

21 BY MR. PARKER:

22 Q. Did Dr. Leffler get back to
23 you by way of e-mail with the 60 that he
24 identified?

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1 A. He did, yes.

2 Q. And has that been preserved,
3 the e-mail?

4 A. The e-mail, I would -- so
5 let me -- hold on.

6 I cannot recall if he sent a
7 list or if I actually algorithmically
8 applied his criteria based on the cases I
9 had.

10 So i believe we -- no, we
11 went through the list of cases. Maybe
12 that was e-mail, and maybe that was
13 phone. I cannot recall. I'm sorry.

14 Q. Now, I'm confused. Doctor,
15 initially you said Dr. Leffler reviewed
16 some cases that generated to 60. Now you
17 seem to be saying that you did an
18 algorithmic analyses after consultation
19 with Dr. Leffler that produced the 60.

20 Which happened?

21 MS. SUTTON: Objection to
22 form. Asked and answered.

23 THE WITNESS: Well, so these
24 are the criteria here. So because

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1 he -- so I created a system where
2 he reviewed each of the MedWatch
3 forms. And so each MedWatch form
4 was abstracted. He reviewed that
5 information. And then he actually
6 identified which symptoms were in
7 each of those MedWatch forms. And
8 then he, you know, followed -- he
9 filled out these forms.

10 And then I think that he
11 gave -- and then I could have gone
12 ahead and made this algorithmic
13 thing. But my recollection is
14 that I -- he gave me a list, yes.

15 BY MR. PARKER:

16 Q. Did Dr. Leffler look at the
17 335 reports?

18 A. He did.

19 Q. Okay. Looked at all 335?

20 A. He did.

21 Q. Okay. All right. We're
22 going to come back to this. But I want
23 to change topics just for a second and
24 talk about some of the things in your CV.

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1 MS. SUTTON: Objection to
2 form. Foundation.

3 THE WITNESS: So the terms
4 that I used in this e-mail are
5 celiac, spruelike enteropathy, and
6 villous atrophy as listed in
7 Number 3.

8 BY MR. PARKER:

9 Q. Okay. You had not begun yet
10 the process of abstracting the MedWatch
11 reports in April of 2016, correct?

12 A. I had not.

13 Q. Okay. And so what was
14 Dr. Leffler's recommendation as to do a
15 really wide grab, to quote you, or a
16 smaller set of terms?

17 MS. SUTTON: Objection to
18 form.

19 THE WITNESS: So you'll see
20 in the follow-up e-mail, he talks
21 about emphasizing the high
22 specificity terms.

23 And as we were going through
24 the process of examining -- so

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1 there's a constellation of
2 symptoms for olmesartan-induced
3 enteropathy. And so we were also,
4 at that time, talking about
5 looking at other terms from his
6 list.

7 BY MR. PARKER:

8 Q. And eventually they whittle
9 down to the ones that we talked about
10 earlier, diarrhea, vomiting, celiac
11 disease?

12 A. So the exact -- so Dan's
13 exact process of coming up to those list
14 of terms for his list of 60 cases which
15 he identified, he came up with those on
16 his own using his clinical judgment for
17 that particular list for the 60.

18 Q. That may be true. But my
19 question is ultimately the list that you
20 both came down to was diarrhea, vomiting
21 or celiac disease, as you stated earlier
22 in your report?

23 A. As combined --

24 MS. SUTTON: Objection to

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1 now five months after the last series of
2 e-mails that we looked at in April --
3 that you're now ready to proceed,
4 correct?

5 A. That is correct. So the --
6 I received the MedWatch forms. One of
7 the employees working for me had entered
8 all of the information into a system so
9 that Dan could confirm the information
10 within that system. And it was very time
11 consuming.

12 Q. Had the 335 files been
13 identified at this point on
14 September 13th?

15 A. So the set of files that I
16 was given to get an understanding of the
17 MedWatch forms that were submitted
18 consistent with -- or that had symptoms
19 that were within the constellation of
20 olmesartan-induced enteropathy and could
21 possibly be included in the highly
22 specific list that Dan came up with, and
23 as he talked about previously, maximizing
24 specificity, yes, they had been received

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1 (Document marked for
2 identification as Exhibit
3 Huftless-15.)

4 BY MR. PARKER:

5 Q. Let me move on to
6 Exhibit 15, which is an e-mail of
7 November 6, 2016.

8 If we flip to the back,
9 Doctor, you will see that you are sending
10 a number of files to Dr. Leffler and his
11 team.

12 Do you see that? It's on
13 your e-mail of November 6th at 7:12 p.m.

14 A. Correct.

15 Q. Now, are these reference
16 files MedWatch reports?

17 A. They are.

18 Q. Okay. And are these
19 MedWatch reports those that were
20 distilled from the 335 after applying
21 Dr. Leffler's more specific terms?

22 MS. SUTTON: Objection to
23 form. Foundation.

24 THE WITNESS: Can you repeat

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1 the question?

2 BY MR. PARKER:

3 Q. Are these MedWatch reports
4 the result of Dr. Leffler's more specific
5 terms that reduced the number from 335 to
6 what we see here?

7 MS. SUTTON: Objection to
8 form. Foundation.

9 THE WITNESS: So these
10 were -- I can't recall the list.
11 So when I went through to make
12 sure that his data abstraction was
13 performed properly and there
14 wasn't missing information and
15 other items, I had sent him the
16 list to go ahead and review the
17 cases.

18 BY MR. PARKER:

19 Q. Doctor, what I'm not
20 understanding is, had the list of 335
21 been narrowed down by this point in
22 November of 2016?

23 MS. SUTTON: Objection to
24 form. Foundation.

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1 THE WITNESS: I mean, I
2 can't recall the dates. So this
3 is a subset of MedWatch forms. I
4 can't recall the exact dates.

5 BY MR. PARKER:

6 Q. You don't recall when, as a
7 result of your collaboration with
8 Dr. Leffler, the 335 files that you had
9 access to on the link that we've
10 discussed, was reduced to 60?

11 MS. SUTTON: Objection to
12 form. Foundation.

13 BY MR. PARKER:

14 Q. Is that correct?

15 A. No, I don't recall the exact
16 date of that happening.

17 Q. Do you recall the month?
18 Was it before this period of time, early
19 November?

20 A. So these were -- I was
21 trying -- based on the entry of the
22 cases, I had questions about the content
23 of the data entry.

24 Q. All right. Let's look at

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1 Q. Total count of others is 60.
2 That makes the 335, correct?

3 A. Correct.

4 Q. And of the total 335 of
5 those -- well, actually, of the 60 for
6 which there was information, 55 or
7 91 percent said there were alternative
8 causes; is that correct?

9 A. So it says yes on this form,
10 that is correct. I know that this was at
11 a different point -- earlier point in
12 their work process because there were
13 conversations -- I think this is one of
14 the conversations that Dan, his team, and
15 I had together to ensure consistency. So
16 we had talked about the symptoms of
17 olmesartan-induced enteropathy, and one
18 of them being diarrhea. And so we were
19 struggling with how the Naranjo scale
20 really applied to this condition, given
21 that one of the symptoms is diarrhea, and
22 diarrhea can have lots of causes.

23 So we were trying to figure
24 out should we take these alternative

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1 causes and say, well, perhaps all of
2 these should have alternative causes,
3 because diarrhea could be caused by
4 anything, or should we take the specific
5 to the cases that are olmesartan-induced
6 enteropathy with respect to a
7 constellation of causes and identify them
8 based on that particular case and that
9 information in the MedWatch form.

10 Q. And -- sorry.

11 A. And my recollection, as they
12 were talking about this, at one point for
13 simplicity, he had told them to mark yes
14 for everything, but then had this deeper
15 discussion about what was going on with
16 Naranjo, as well as how it actually
17 applies to this particular condition.

18 And, you know, I actually
19 don't know if they changed their work
20 product, because I didn't rely on this
21 question when I did the WHO causality
22 assessment. I relied on three individual
23 questions instead, which actually related
24 to what their determination was, related

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1 to comorbidities had an effect, other
2 medications had an effect, or allergies
3 had an effect.

4 One actually needed more
5 specific, as it was collecting
6 information from each of those different
7 potentiality alternative causes. Rather
8 from the Naranjo scale question, which
9 Dan and I had -- when we talked in May of
10 2016, were really struggling with how
11 this would apply to this actual setting.

12 So because Naranjo is really
13 the standard for this, I felt obliged to
14 collect this information, but also make
15 sure that the information I collected
16 could be used for the WHO causality
17 assessment.

18 And ultimately I felt that
19 the WHO causality assessment was more
20 applicable given the limited
21 applicability of Naranjo to
22 olmesartan-induced enteropathy.

23 And the question to me
24 really that were most important to this

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1 were assessing temporality, assessing
2 dechallenge, assessing rechallenge, and
3 then of course, ruling out the
4 alternative causes based on those other
5 questions.

6 MR. PARKER: Move to strike.

7 MS. SUTTON: Objection.

8 BY MR. PARKER:

9 Q. Doctor, after that deeper
10 conversation that you described, your
11 team, with Dr. Leffler, went from 55 of
12 the 60 files having alternative causes,
13 to zero, after the deeper conversation,
14 correct?

15 MS. SUTTON: Objection.

16 Form. Misstates testimony.

17 BY MR. PARKER:

18 Q. Is that right?

19 A. So I don't know at which
20 point this happened in the work process.
21 And I have relied upon three questions
22 that are actually captured, three
23 alternative causes, which is the rule of
24 comorbidities, medications, and

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1 allergies.

2 I have not relied on this
3 question in my causality assessment.

4 Q. And that's -- no question
5 about that, Doctor.

6 But you did send this -- you
7 chose the Naranjo scoring system to send
8 to Dr. Leffler and his team and asked him
9 to score the reports, correct?

10 A. Correct, with the
11 recognition that I would be able to use
12 the questions from Naranjo to also
13 perform the WHO causality assessment. So
14 you can see from my prior literature that
15 I've also performed the WHO causality
16 assessment and Naranjo examining the
17 relationship between treatments for
18 Crohn's disease and hepatosplenic T-cell
19 lymphoma.

20 Q. And the truth of the matter
21 is if you had applied the Naranjo scoring
22 system to these cases, you would not have
23 generated a high enough score to be able
24 to say these were in the probable rank,

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1 correct?

2 MS. SUTTON: Objection to
3 form. No foundation.

4 THE WITNESS: If you look
5 at --

6 BY MR. PARKER:

7 Q. Is that correct?

8 A. -- Dr. Risch's report --

9 MS. SUTTON: Let her answer.

10 THE WITNESS: -- you will
11 see that Dr. Risch applies the
12 Naranjo scale, and he comes up
13 with an assessment of probable.

14 BY MR. PARKER:

15 Q. Oh, really? Okay.

16 A. He does.

17 Q. That's -- so my question is,
18 did you choose not to use Naranjo because
19 you couldn't get a high enough number?

20 MS. SUTTON: Objection to
21 form.

22 THE WITNESS: No, I did not.
23 I chose not to use Naranjo because
24 of the conversations that I had

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1 been having since May of 2016 with
2 Dr. Leffler about the
3 applicability of Naranjo to this
4 particular setting.

5 You can see in the published
6 peer-reviewed literature I've had
7 similar difficulties and
8 frustrations with Naranjo as it
9 relates to medications and
10 hepatosplenic T-cell lymphoma and
11 Crohn's disease.

12 Actually, if you apply the
13 Naranjo scale -- let's see, I have
14 this.

15 All right. So based on the
16 conversations that Dan and I had
17 about the limited applicability of
18 the Naranjo scale, you would see
19 that some of the responses would
20 be fixed for the participants.

21 Is it okay if I read to you?

22 BY MR. PARKER:

23 Q. No, I really don't -- that's
24 not responsive to my question.

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1 correct?

2 A. So that is correct. So he
3 and I had a conversation about this.

4 Q. That's all I'm asking.

5 A. Can I finish?

6 Q. No, because all I'm asking
7 right now, Doctor, is as of this date,
8 was Dr. Leffler still attempting to use a
9 Naranjo scale?

10 A. So I saw that on the
11 comorbidities effect, medications effect
12 and allergies effect, there remained
13 information that was missing or not
14 mentioned.

15 So I sent him this
16 information, and then he and I actually
17 had a phone call, and we talked about
18 what it meant when something was missing
19 or not mentioned.

20 Based on our conversation,
21 anytime something was listed as missing
22 or not mentioned it was no. And the
23 reason why is that there were so many of
24 these where the comorbidities effect,

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1 medications effect, and allergies effect
2 was a no in his mind. It was more
3 efficient for him to just communicate
4 that to me that not mentioned and missing
5 was a no, rather than him going through
6 and checking a bunch of boxes.

7 So he's a busy clinician.
8 For him to go through and double-check a
9 bunch of boxes wasn't efficient. So we
10 had a verbal communication about this.

11 And you'll see in here one
12 of them is listed as no, no. If
13 anything, that just reflects
14 inconsistencies in his team's approach,
15 which you saw earlier in their
16 conversations when he was getting
17 everything on board and being consistent,
18 so that his final determination, based on
19 a conversation with me, was that missing
20 and not mentioned meant no.

21 You'll also see ones labeled
22 as yes which Dr. Leffler reviewed and
23 considered to be yes, that the
24 comorbidities had an effect, or the

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1 medications had an effect.

2 Q. So if there's no information
3 provided in the MedWatch report about
4 whether a patient was using other drugs
5 that might explain the reaction and no
6 information is given about other
7 comorbidities, you didn't score this as
8 not mentioned. You said no, negative,
9 there were no other comorbidities, there
10 were no other possible drugs that might
11 have influenced or might be explaining
12 the effect.

13 MS. SUTTON: Objection.

14 BY MR. PARKER:

15 Q. You changed not mentioned
16 into a definitive no, correct?

17 A. I'm sorry for interrupting.

18 MS. SUTTON: Objection to
19 form. Compound.

20 THE WITNESS: So the -- my
21 understanding is that you're
22 asking me to generalize about the
23 content of all of the MedWatch
24 forms, which I can't do. We can

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1 talk about specific forms and
2 review them. But I can't
3 generalize to all the forms.

4 So if you look at these
5 MedWatch forms, they describe
6 patients who have multiple
7 comorbidities. All right.

8 So it was Dr. Leffler's, a
9 gastroenterologist, assessment
10 that there is no impact of
11 comorbidities, medications, or
12 allergies. So the information
13 provided on those MedWatch forms
14 was actually entered by the
15 manufacturer.

16 Dr. Leffler, to my
17 understanding, also had source
18 files, which I believe is notes or
19 other sources or something like
20 that, that goes along with the
21 MedWatch forms. I've never seen
22 the source files. I have a
23 superficial understanding of what
24 the content of information that

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1 was there, based on what he was
2 actually able to review.

3 But he used the content in
4 the MedWatch form as well as those
5 source files to come to a
6 determination of no -- to come to
7 a determination that anytime it
8 said not mentioned or missing,
9 that was in fact a no.

10 BY MR. PARKER:

11 Q. Okay. Doctor, define for me
12 what general causation means to you.

13 A. What general causation means
14 to me?

15 Q. Correct.

16 A. So I view causation from the
17 perspective of epidemiology. So I'm
18 looking to see if an exposure has a
19 causal effect or a causal relationship on
20 an outcome. In this case, olmesartan and
21 the -- I guess you would say the
22 constellation of symptoms consistent with
23 olmesartan-induced enteropathy.

24 To inform that relationship

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1 between olmesartan and olmesartan-induced
2 enteropathy, I used a variety of
3 evidence. Or I'm sorry. I used a
4 variety of information.

5 So I used the Bradford Hill,
6 which I referred to as criteria but
7 actually isn't criteria. It's something
8 that's used where you can look at
9 different categories and make a
10 determination to help you inform your
11 assessment of the causal relationship.
12 This was something that was originally
13 created for Bradford Hill to come up with
14 for a relationship between smoking and
15 lung cancer.

16 So rather than basing
17 causation on one element, you are to --
18 you take into consideration a variety of
19 items. And then there's no scoring or
20 anything like that, in aggregate decide,
21 based on your expert opinion, is there a
22 relationship.

23 To inform the Bradford Hill
24 criteria, I conducted a systematic review

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1 that we've been talking at least briefly
2 about the methods of.

3 I also reviewed case report
4 forms. So I reviewed -- so I reviewed --
5 I conducted a systematic review which
6 included identifying randomized trials,
7 nonrandomized studies, and case report
8 forms and case series.

9 So the reason why I included
10 those cases is because there wasn't very
11 much information from the literature
12 related to other study designs. Using
13 cases to inform a causal opinion is
14 actually something that is in -- for
15 looking at a systematic review, is in
16 both the Cochrane methods guide, as well
17 as the Evidence-Based Practice Center's
18 method guide. It's referred to in
19 Strom's Pharmacoepidemiology, and also
20 the FDA refers to using case reports in
21 assessing causation.

22 So I used all of that
23 information, both from the randomized
24 trials, the nonrandomized studies, the

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1 THE WITNESS: So that's a
2 clinical question. You're asking
3 how -- I guess I don't
4 understand -- can you ask the
5 question again?

6 BY MR. PARKER:

7 Q. Okay. I'll rephrase it this
8 way. Doctor, what did you understand
9 your charge to be when you were retained
10 by Dr. Leffler on behalf of counsel?
11 What was the question that you were asked
12 to answer?

13 MS. SUTTON: Objection to
14 form. Foundation.

15 THE WITNESS: Is there a
16 relationship between olmesartan
17 and the signs -- and the
18 constellation of symptoms
19 consistent with olmesartan-induced
20 enteropathy?

21 And when did I think that
22 causal conclusion could have been
23 made?

24 BY MR. PARKER:

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1 A. You did. Thank you. Good
2 job.

3 Q. All right. Thank you. Now,
4 did you construct a case definition?

5 A. So for the MedWatch forms
6 which I relied upon, the determination of
7 which of those were cases of
8 olmesartan-induced enteropathy was
9 decided by Dr. Leffler, based on his
10 expert opinion.

11 Q. So you did not yourself
12 develop a case definition; is that
13 correct?

14 A. I did not.

15 MS. SUTTON: Objection.
16 Misstates testimony and the
17 report.

18 THE WITNESS: So I -- for
19 the MedWatch forms, I relied upon
20 Dr. Leffler's assessment. And
21 then for the case reports from the
22 literature, I relied upon the peer
23 review process of the clinician
24 submitting those case reports to

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1 thought to have and what the FDA has used
2 as an indicator of these symptoms in
3 their Mini-Sentinel study.

4 Q. All right. Doctor, early in
5 the answer, but it was a few pages ago,
6 you made the statement that these are not
7 the diagnostic criteria. Tell me,
8 Doctor, what are the diagnostic criteria
9 for spruelike enteropathy associated with
10 olmesartan use?

11 MS. SUTTON: Object to form.

12 THE WITNESS: So I'm not a
13 clinician. I do not make
14 diagnoses, although I am aware of
15 the constellation of symptoms
16 that, based on my understanding of
17 the literature, is associated with
18 olmesartan-induced enteropathy.

19 BY MR. PARKER:

20 Q. Then how can you make the
21 statement these are not the diagnostic
22 criteria?

23 MS. SUTTON: Objection to
24 form. Misstates testimony.

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1 That's based on your request for me to
2 answer the question. I'm giving you that
3 as an epidemiologist.

4 Q. I understand that, Doctor,
5 but in order as an epidemiologist to
6 answer a question whether a drug is
7 causing an outcome, you sure as heck have
8 to know what the outcome is so you know
9 what you're looking at, right?

10 MS. SUTTON: Objection to
11 form.

12 THE WITNESS: That is --
13 thank you.

14 That is why I relied upon a
15 clinician to come to the
16 assessment of the
17 olmesartan-induced enteropathy
18 cases.

19 I didn't do that myself. I
20 relied upon Dr. Leffler to make
21 that decision.

22 Similarly, from the
23 literature, I relied upon the
24 clinician who submitted those

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1 cases to the literature and the
2 peer review process to determine
3 that those were cases of
4 olmesartan-induced enteropathy.

5 BY MR. PARKER:

6 Q. So it sounds like your
7 understanding of the literature is if a
8 patient presents with any GI complaint,
9 no matter how minimal, if it goes away,
10 if they stop using olmesartan, that's
11 olmesartan enteropathy, correct?

12 MS. SUTTON: Objection.
13 Misstates testimony.

14 THE WITNESS: If the
15 clinician considers the case to be
16 olmesartan-induced enteropathy, it
17 is a case of olmesartan-induced
18 enteropathy.

19 BY MR. PARKER:

20 Q. Okay. That's definitive.
21 So if a patient comes in --

22 MS. SUTTON: Objection to
23 form and to the continued
24 commentary on the --

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1 My assumption with that sentence is
2 they're talking about what's happening
3 mucosally and not something that needs to
4 be confirmed.

5 Q. My question is, I think
6 you've answered it, but I wasn't sure,
7 that in order to confirm a diagnosis of
8 spruelike enteropathy, there must be
9 clinical resolution of symptoms, correct?

10 MS. SUTTON: Objection to
11 form. Asked and answered.

12 THE WITNESS: So, I mean,
13 I'm not a clinician. So I trust
14 that if a clinician says that a
15 case is spruelike enteropathy
16 associated with olmesartan and the
17 clinician says that the patient
18 has this, and particularly if
19 they've done a withdrawal, that
20 their understanding in that
21 clinician's assessment of the
22 resolution or the decrease in --
23 the improvement in symptoms would
24 be a confirmation of diagnosis if

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1 the clinician says that.

2 BY MR. PARKER:

3 Q. You just added something to
4 my question. That's what I want to make
5 clear. Doctor, if there has not been
6 resolution of clinical symptoms but some
7 improvement, does that confirm the
8 diagnosis?

9 A. So my understanding is that
10 it is possible for there to be such
11 damage that the patient's mucosa is
12 permanently damaged; therefore, they may
13 require additional treatments over time
14 because of that permanent damage. And it
15 may never resolve if the olmesartan has
16 led to a biologic process that is
17 permanent.

18 Q. Do you understand that as
19 used in this document, in this paper,
20 clinical resolution to refer to
21 histopathologic changes?

22 A. This -- well, this sentence
23 itself is referring to clinical
24 resolution --

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1 assuming that given the title of a
2 director of a center might assist one in
3 getting grants?

4 A. That is true, yes. And the
5 expectation is that I will write grants
6 associated with gastroenterology and
7 epidemiology for -- as part of my work at
8 Johns Hopkins.

9 Q. All right. So let's go back
10 to this exhibit. What did I say the
11 number was? Exhibit 23.

12 Let's look at Table 12.2.A,
13 entitled "Levels of Quality of a Body of
14 Evidence in the GRADE Approach."

15 Do you see that, Doctor?

16 A. I do.

17 Q. Okay. And I take it since
18 you used this approach, you subscribe and
19 agree with their ranking?

20 A. So I have used the GRADE
21 approach for other exposure-outcome
22 relationships. And those actually were
23 when it was a large body of evidence or
24 there were numerous studies that had

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1 talking about using different
2 types of these evidence in
3 different settings, depending on
4 both the question as well as the
5 amount of information available.

6 MR. PARKER: Move to strike.

7 MS. SUTTON: Oppose.

8 BY MR. PARKER:

9 Q. Doctor, specifically, do you
10 agree with Table 12.2.A of the Cochrane
11 collaboration that a case series/case
12 reports are described as very low in
13 quality rating, yes or no?

14 A. Within the GRADE framework,
15 that is how the GRADE tool assigns them
16 in this -- in the GRADE framework as is
17 represented in this table.

18 Q. Okay. Let's move on then.
19 Let's talk about --

20 A. But in the Cochrane
21 report -- so in the Cochrane methods
22 guide, if you look at other sections, it
23 talks specifically about when to use
24 different types of evidence in what

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1 Q. And you agree that what
2 you've done here is data mining? I care
3 not about other people. I care only
4 about you. Would you agree that what
5 you've done here is data mining?

6 MS. SUTTON: Objection to
7 form. Asked and answered.

8 THE WITNESS: I assessed
9 exposure-outcome relationship
10 using the FDA adverse event
11 reporting system, which is
12 considered to be a data mining
13 tool, in combination with other
14 evidence. That is correct.

15 BY MR. PARKER:

16 Q. Doctor, do you hold the
17 opinion that olmesartan causes celiac
18 disease?

19 A. I -- based on this, I hold
20 the opinion that olmesartan causes a
21 constellation of symptoms, some of which
22 are consistent with celiac disease, so
23 celiac-like symptoms. Does it cause
24 celiac disease itself? No, celiac

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1 disease is a distinct entity.

2 Q. Doctor, do you know what the
3 prevalence of celiac disease in the U.S.
4 population?

5 A. So the prevalence of celiac
6 disease in the United States population
7 varies on the population survey. So
8 there aren't a lot of great estimates of
9 the prevalence or incidence, for that
10 matter, of celiac disease.

11 But my best -- my
12 understanding of the literature is the
13 best guess that prevalence is about 1
14 percent.

15 Q. Okay. And, Doctor, you
16 wrote in your report that beginning in
17 2006 approximately one million people
18 were filling prescriptions for olmesartan
19 each year, correct?

20 A. So over a million. My
21 recollection is over a million people,
22 yes.

23 Q. So the background rate of
24 celiac disease in the population of

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1 with drugs. So for example, rheumatoid
2 arthritis, if it is important to adjust
3 for NSAIDs, which you're implying that it
4 is --

5 Q. I'm saying all drugs,
6 Doctor. I'm not focused on just NSAIDs.

7 A. Okay. So if you're
8 interested in adjusting for a drug that
9 is associated with only the outcome,
10 enteropathy, and not associated with the
11 exposure of olmesartan, one method of
12 doing that would be to adjust for the
13 comorbidities that it's associated with.

14 As you know, NSAIDs are
15 over-the-counter medications. Many
16 people will take NSAIDs at some point in
17 their life. And most studies, even
18 randomized controlled trials, aren't
19 going to be able to capture NSAID use
20 because it's such a ubiquitous exposure.

21 MR. PARKER: Move to strike.

22 BY MR. PARKER:

23 Q. Doctor, my question to you
24 again was, point to me in this paper the

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1 language that you're relying upon to say
2 that this group of investigators adjusted
3 for alternate drug exposures?

4 MS. SUTTON: Objection to
5 form. Misstates testimony.

6 THE WITNESS: In this paper,
7 they do not adjust for alternate
8 drugs, but they do however adjust
9 for comorbidities --

10 BY MR. PARKER:

11 Q. Where?

12 A. -- that are often associated
13 with alternate drugs.

14 Q. I've asked you now four
15 times. Show me what you're relying upon.

16 A. About the comorbidities?

17 MS. SUTTON: Object to the
18 colloquy.

19 BY MR. PARKER:

20 Q. Yes, ma'am. And the
21 specific comorbidities.

22 A. Sure. So this would be Page
23 1665.

24 Q. I have different page

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1 Q. Let's go on to Exhibit 27
2 which is the Padwal study.

3 Doctor, if you could turn,
4 please, to Page 25 of your report. Tell
5 me when you have it.

6 Are you with me, Doctor?

7 A. I am on Page 25 of my
8 report, yes. Thank you for your
9 patience.

10 Q. Doctor, the Padwal study was
11 published in Hypertension; is that
12 correct?

13 A. So it's Pages 24 to 25.

14 Q. No. The paper, the exhibit
15 that I just gave to you. Right here,
16 Doctor.

17 A. Yeah, so this is published
18 in May of 2014 in Hypertension. That's
19 correct.

20 Q. And how would you describe
21 the quality of the journal Hypertension?

22 A. It is a high quality
23 journal, to my understanding, of the
24 hypertension literature, which I'm --

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1 Q. Okay. And you describe this
2 study written in as -- did you say high
3 powered journal? Was that the phrase you
4 used?

5 A. It is a respected journal
6 among the clinical community, is my
7 understanding.

8 Q. Okay. And you wrote, "Due
9 to the lack of specificity of the
10 symptoms of olmesartan-induced
11 enteropathy and the lack of examination
12 of celiac disease, malabsorption, or
13 composite symptoms associated with
14 enteropathy, this study does not
15 contribute to the evidence."

16 Did I read it correctly?

17 A. So --

18 Q. Did I read it correctly,
19 Doctor?

20 A. That is correct.

21 Q. So Hypertension and the peer
22 reviewers agreed to publish a paper that,
23 in your words, does not contribute to the
24 evidence of whether olmesartan causes

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1 accurate in my statements.

2 Q. Doctor, you're just rambling
3 on something that's not answering my
4 question.

5 MS. SUTTON: Objection.

6 BY MR. PARKER:

7 Q. You're just wasting time.

8 MS. SUTTON: Objection for
9 the colloquy. It's inappropriate,
10 and it's not true.

11 MR. PARKER: You know what,
12 maybe you're right, but neither
13 are her responses, Tara. She's
14 just talking.

15 BY MR. PARKER:

16 Q. You're not answering my
17 questions.

18 MS. SUTTON: Objection to
19 your colloquy.

20 BY MR. PARKER:

21 Q. So let me go on, Doctor. Do
22 you know what propensity scoring is?

23 A. I do know what propensity
24 scoring is.

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1 Q. Was it used in the Padwal
2 study?

3 A. Yes.

4 Q. Was it used in the French
5 study?

6 A. It was not. And if --

7 Q. So that's all my question.
8 Was it used --

9 A. Propensity scoring is used
10 as an option for confounder adjustment.

11 Q. All my question -- you
12 understand my question was simply, did
13 the French use propensity scoring?

14 A. No, they did not.

15 Q. Okay. Do you know why
16 people like yourself use propensity
17 scoring?

18 A. Yes, I do.

19 Q. And is propensity scoring a
20 methodological means by which to reduce
21 potential confounding?

22 A. It is an alternative and an
23 equally good alternative to including all
24 available potential confounders in a

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1 Q. Doctor, that's yes or no.

2 MS. SUTTON: Objection to

3 form.

4 THE WITNESS: So if you will

5 see that the studies from

6 Columbia, I say that the study

7 does not contribute to the

8 evidence. That is what it says.

9 BY MR. PARKER:

10 Q. Thank you.

11 A. And as you'll see in my

12 methods section when I describe the

13 nonrandomized studies that I'm going to

14 include, I'm going to place weight on the

15 studies that do account for confounding

16 and I -- one of --

17 Q. But not the Padwal?

18 A. -- the confounders is

19 comorbidities.

20 The issue -- actually, the

21 confounding is excellent in Padwal. My

22 issue with Padwal is not his adjustment

23 for confounding. It's that he's studying

24 gastrointestinal disorders. I actually

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1 randomized trials, and there were 191
2 clinical trials associated with
3 olmesartan.

4 Q. All right. And 20 of them
5 were more than one year in length,
6 correct?

7 A. That's correct. There's a
8 discrepancy between the clinical trials
9 on clinicaltrials.gov and then those
10 reported in the literature.

11 And these are trials by --
12 in the clinicaltrials.gov are by any
13 sponsor.

14 Q. And that body of evidence
15 does not, to use your words, contribute
16 to the evidence, correct?

17 MS. SUTTON: Objection to
18 form and foundation.

19 THE WITNESS: So looking at
20 clinicaltrials.gov, which is what
21 we started with, that does not
22 contribute to the evidence. The
23 reason why is because none of
24 those studies were designed and

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1 included olmesartan-induced
2 enteropathy as a primary and
3 secondary outcome.

4 So you can actually look.
5 You would perhaps think that given
6 the safety communication and the
7 best practices in performing
8 pharmacovigilance, that the
9 company may have considered
10 including olmesartan-induced
11 enteropathy in its symptoms as a
12 primary and secondary outcome in
13 its subsequent trials, and that
14 has not happened to date.

15 That's what, to me, the
16 clinicaltrials.gov results are
17 showing, is that there's been no
18 study that's been designed to
19 assess gastrointestinal events in
20 general, according to the publicly
21 posted trial on
22 clinicaltrials.gov.

23 In terms of the randomized
24 trials, 191 trials from the 227

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1 publications -- so these trials --
2 well, for one, 79 percent of them
3 didn't report on gastrointestinal
4 adverse events at all, which
5 suggests potential publication
6 bias.

7 So we only have 21 percent
8 of all the trials even publishing
9 anything remotely and potentially
10 related to olmesartan-induced
11 enteropathy. But none of them
12 actually is studying
13 olmesartan-induced enteropathy.

14 We know it's comprised by a
15 composite group of symptoms. It's
16 not just one symptom at a time.
17 They're reporting their outcomes.
18 They're only doing one symptom at
19 a time. And that's not
20 representative of
21 olmesartan-induced enteropathy
22 based on my understanding of the
23 clinical literature.

24 BY MR. PARKER:

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1 Q. So the long and short of it,
2 for all that explanation, is that the 191
3 clinical trials addressed in 227
4 publications, 20 of which were done for
5 longer than one year, do not contribute
6 to the evidence that we are discussing of
7 whether olmesartan causes spruelike
8 enteropathy, correct?

9 A. Correct.

10 Q. Thank you.

11 A. Because they do not assess
12 the outcome of interest.

13 (Document marked for
14 identification as Exhibit
15 Huftless-28.)

16 BY MR. PARKER:

17 Q. All right. Let's move on to
18 Exhibit 28, please.

19 Doctor, you got 28?

20 A. Yes, I do.

21 Q. Doctor, 28 is the MedWatch
22 report for MedWatch Report Number
23 2006-3369, correct?

24 A. That's correct.

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1 (Document marked for
2 identification as Exhibit
3 Huftless-29.)

4 BY MR. PARKER:

5 Q. Okay. Very good. Well,
6 then let's take a copy of that and mark
7 it as 29. Doctor, before you put that in
8 your report, did you actually read the
9 paper?

10 A. I did to the best of my
11 ability. So I am not an immunologist or
12 basic scientist. I am an epidemiologist.

13 Q. I understand that. You've
14 told me that many times today.

15 A. Correct.

16 Q. You did, when you read it,
17 felt that this supported your claim that
18 olmesartan-induced enteropathy exists in
19 rats, right?

20 A. So when using --

21 Q. Is that just what you said,
22 Doctor?

23 A. My one-sentence summary of
24 reading this paper to the best of my

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1 ability is that it says
2 olmesartan-induced enteropathy exists in
3 rats, yes.

4 Q. Now, you read some of the
5 reports of the defense experts, some of
6 whom talked about this paper, correct?

7 A. That is correct.

8 Q. And they mention that there
9 was a paper published by this same group
10 a year earlier that reached, so they
11 felt, a very different conclusion. Do
12 you recall that?

13 A. Yes. I recall -- I can't
14 remember which the experts talked about
15 that. But both of these papers are
16 published in peer-reviewed journals. So
17 they've undergone a peer review process.
18 I trusted that peer review process when
19 assessing plausibility, which is to say,
20 is it plausible that there's a biologic
21 mechanism. And this, to me, was
22 supportive of plausibility.

23 Q. Doctor, part of your
24 review -- excuse me. Part of the process

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1 of doing a Cochrane systemic review is
2 coming to an assessment of the quality of
3 a study; is that correct?

4 A. Yes, that's true. It's a
5 systematic review.

6 Q. Now, when you read the
7 defense experts' report and they
8 highlighted this group had published a
9 paper a year earlier, did you pull it out
10 and read that paper?

11 A. So I actually --

12 Q. That's yes or no.

13 A. So at that time, no. But I
14 had previously reviewed that paper when I
15 had identified this and I was looking at
16 plausibility. That is correct.

17 Q. Can you show me either in
18 your reliance list -- maybe I missed it.
19 It wasn't initially referenced in your
20 reliance paper, the 2014 paper, is it?

21 A. I am not aware because it is
22 not cited in my paper.

23 Q. Right.

24 A. So I think there were about

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1 5,000 articles identified by my search.
2 So not all of those 5,000 articles is in
3 my reliance list.

4 Q. I know. But you just told
5 me that you actually read the 2014 paper
6 before you did your report.

7 A. I read a lot of papers and
8 reviewed a lot of papers. If you would
9 like the list of all the 5,000 studies, I
10 can give them to you.

11 Q. No, Doctor, just answer my
12 question. Did you read the 2014 paper?

13 A. I reviewed the -- to the
14 best of my knowledge, I had reviewed the
15 2014 paper as part of my systematic
16 review process for this report. That is
17 correct.

18 (Document marked for
19 identification as Exhibit
20 Huftless-30.)

21 BY MR. PARKER:

22 Q. So just so the record is
23 clear, I'm going to give you Exhibit 30,
24 which is the 2014 paper.

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1 MS. SUTTON: Thank you.

2 MR. PARKER: Sure.

3 BY MR. PARKER:

4 Q. And it's your testimony that
5 before you wrote your report, you
6 actually had knowledge of and had read
7 the 2014 paper as well as the 2015 paper,
8 right?

9 MS. SUTTON: Objection to
10 form.

11 THE WITNESS: I have -- yes,
12 I have reviewed both of these
13 papers. That is correct.

14 BY MR. PARKER:

15 Q. Before your report?

16 A. Before my report, yes. And
17 so this -- but what we're talking about
18 here is not for me to do a systematic
19 review of the basic science literature,
20 which I'm in fact not qualified to do a
21 basic science review of -- a systematic
22 review of the basic science literature.

23 Q. What I'm --

24 A. What I've been trying to

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1 assess for the Bradford Hill criteria is
2 plausibility.

3 And so the -- what I used
4 for that is, is the association
5 consistent with other knowledge,
6 including mechanism of action and animal
7 experiments?

8 And so as part of that I
9 went to the literature and I saw, is it
10 possible that there is a relationship
11 between these based on the animal
12 literature.

13 And this 2015 paper that I
14 saw says the olmesartan-induced -- my
15 assessment of that is it says
16 olmesartan-induced enteropathy exists in
17 rats, which suggests plausibility.

18 Did I do a systematic review
19 of the literature? No. Did I cite every
20 single basic science article that I've
21 identified? No. Did any of these
22 experts do a systematic review of the
23 basic science literature? Not that I can
24 tell from their reports.

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1 talk more definitively about the
2 pathology.

3 BY MR. PARKER:

4 Q. I'm looking at whether or
5 not you were selective in your citation
6 to literature.

7 When you read the 2014
8 paper, you saw that in that experiment
9 involving 80 rats they concluded that
10 olmesartan reduced inflammation in the
11 gut of the rats, did not cause it,
12 correct?

13 A. Can you repeat the question,
14 please?

15 Q. When you read the 2014
16 paper, you -- or you saw that the
17 investigators reported that using
18 olmesartan in that group of 80 rats
19 reduced inflammation in the gut, did not
20 cause it?

21 A. So their conclusion, yes, is
22 about reducing inflammation. That is
23 correct.

24 Q. And in the 2015 paper after

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1 form. Mischaracterizes testimony.

2 THE WITNESS: So I'm an
3 epidemiology. I'm not a basic
4 scientist. And addressing the
5 Bradford Hill criteria for
6 plausibility, I went to the
7 literature to see if there was
8 anything about mechanism of action
9 in animal experiments about the
10 relationship between olmesartan
11 and enteropathy.

12 This particular paper, to
13 me, seemed to suggest that there
14 is a plausibility -- a plausible
15 relationship between olmesartan
16 and enteropathy in this rat model.

17 This is a peer-reviewed
18 paper. I trust the peer review
19 process as a person who
20 participates in it, so I trust
21 that to be true and suggestive of
22 plausibility when using the
23 Bradford Hill criteria.

24 BY MR. PARKER:

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1 of you. She has a copy.

2 BY MR. PARKER:

3 Q. I'm sorry, Doctor. I didn't
4 mean to interrupt you that time. I have
5 previously. Apologies. So anyway, in
6 all seriousness, let's go back.

7 Doctor, so how did the data
8 in this study, not their discussion, but
9 how did the data show consistency with
10 other knowledge, including mechanism of
11 action and animal experiments?

12 A. So this is a study about
13 cell lines taken from humans. It is
14 talking about mechanism of action. As
15 you can see, the aim is to determine the
16 mechanistic similarities of
17 olmesartan-associated enteropathy with
18 celiac sprue. And so this is a paper by
19 two of the co-authors, Rubio-Tapia and
20 Murray. So those were the individuals
21 associated with the case series by
22 Rubio-Tapia.

23 And my assumption is they
24 followed up on their finding from a case

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1 series to go take this and look and see
2 is there a mechanistic action. And we
3 have this paper.

4 So that's what they
5 attempted to do to assess that mechanism.

6 Again, this is from the
7 peer-reviewed literature from Elementary
8 Pharmacology and Therapeutics.

9 And you'll see that again
10 because of my -- I'm an epidemiologist.
11 I have a limited ability to assess the
12 information from the literature, that
13 there are quotation marks on my
14 plausibility assessment. And that
15 quotation is in fact the conclusion from
16 the abstract of this paper, again,
17 trusting the peer review process.

18 Q. Okay. So, Doctor, you're
19 going to tell me that it is beyond your
20 area of qualifications and expertise to
21 address the methodological strength and
22 weaknesses of this study; is that
23 correct?

24 A. So this is a study about --

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1 Q. I know what it's about. Is
2 it beyond your ability and expertise to
3 talk about the experimental strengths and
4 the weaknesses of this study?

5 A. It is beyond my ability,
6 yes.

7 Q. Okay. Did you consult with
8 anyone to figure out whether the dosages
9 that were used, the concentrations that
10 were used, were comparable to what a
11 human being will see if given therapeutic
12 levels of olmesartan?

13 MS. SUTTON: Objection to
14 form. Foundation.

15 THE WITNESS: No, I did not.
16 But it's my understanding that
17 frequently in animal studies, the
18 goal is not to -- I'm sorry.
19 This's not an animal study. This
20 is a cell line study. The doses
21 are not necessarily always
22 comparable to humans, that
23 sometimes, in fact, extreme doses
24 are used intentionally.

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1 a good point, can we take a break.

2 We've been a little over an hour?

3 MR. PARKER: Sure, sure.

4 MS. SUTTON: Thanks.

5 (Short break.)

6 BY MR. PARKER:

7 Q. Doctor, please turn to Page
8 6 of your report. You wrote on Page 6,
9 in summary, "It is my opinion to a
10 reasonable degree of scientific certainty
11 that there is sufficient evidence to
12 establish a causal relationship between
13 olmesartan and enteropathy.

14 "There is consistent
15 evidence from MedWatch case reports and
16 signals from FAERS that this causal
17 association was established in 2006."

18 I've read correctly your
19 conclusion; is that correct, Doctor?

20 A. That is correct.

21 Q. And the conclusion with
22 respect to the MedWatch case reports are
23 based on the eight MedWatch reports that
24 you reference on Page 5, the top of

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1 Page 5; is that correct?

2 A. That is correct.

3 (Document marked for
4 identification as Exhibit
5 Huftless-34.)

6 BY MR. PARKER:

7 Q. Go ahead and identify those.
8 So Exhibit 34 is a 2004-2638.

9 (Document marked for
10 identification as Exhibit
11 Huftless-35.)

12 BY MR. PARKER:

13 Q. Exhibit 35 is 2005-0427.

14 (Document marked for
15 identification as Exhibit
16 Huftless-36.)

17 BY MR. PARKER:

18 Q. Exhibit 36 is 2006-5321.

19 (Document marked for
20 identification as Exhibit
21 Huftless-37.)

22 BY MR. PARKER:

23 Q. Exhibit 37 is 2006-5527.

24 (Document marked for

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1 your report a MedWatch-by-MedWatch
2 assessment using the WHO criteria which I
3 marked as Exhibit 33?

4 A. In my report, not to my
5 recollection.

6 Q. Now, your conclusion that
7 causation was proven based on these eight
8 reports in 2006 is based, as I understand
9 it, on what Dr. Leffler told you,
10 correct?

11 MS. SUTTON: Objection.
12 Misstates the report. No
13 foundation.

14 THE WITNESS: So Dr. Leffler
15 identified the list of certain
16 olmesartan -- I'm sorry. He
17 identified the list of cases of
18 olmesartan-induced enteropathy
19 that met those criteria on --
20 based on his clinical judgment.

21 In his clinical judgment,
22 based on a differential diagnosis
23 of the information he had based on
24 the MedWatch forms and source

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1 forms, was these were serious
2 cases with evidence of rechallenge
3 that had symptoms of celiac,
4 diarrhea, or vomiting.

5 I used these cases as a case
6 series, which is consistent with
7 good pharmacoepidemiology
8 practice, to make a determination
9 that there is sufficient
10 information on these rechallenge
11 cases to determine general
12 causation in 2006.

13 BY MR. PARKER:

14 Q. Doctor, did you attempt to
15 use Naranjo or WHO to evaluate each of
16 these eight cases?

17 A. Did I evaluate the clinical
18 characteristics of the cases?

19 Q. Did you go through, as we
20 discussed before, each of these cases,
21 and apply either/or, the Naranjo scaling
22 or the WHO criteria, for each of these
23 eight cases?

24 A. So based on the responses

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1 to -- that Dan -- that Dr. Leffler had in
2 his individual review of each of these
3 cases that are serious rechallenge cases
4 with symptoms of olmesartan-induced
5 enteropathy, I took the information based
6 on the information he gave me, and I came
7 to -- I created a WHO causality
8 assessment for each case.

9 I then used the information
10 about each of those cases in aggregate as
11 a case series and made a determination
12 about general causation.

13 Q. Doctor, I'll call for the
14 production of that WHO assessment,
15 because that's not reflected in your
16 report anywhere, is it?

17 A. Not to my recollection. The
18 individual level information is not.

19 MS. SUTTON: That
20 information was produced to
21 defense.

22 MR. PARKER: It either is or
23 isn't.

24

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1 did not search for medications
2 other than olmesartan in my search
3 for cases.

4 BY MR. PARKER:

5 Q. Let me see if I understand
6 that. In then addressing a criteria, the
7 Bradford Hill criteria specificity, you
8 rely upon your data mining exercise,
9 correct, to say it's unique? That's what
10 you state here, right, bottom of Page 8?

11 A. Yes, I do.

12 Q. But you never then, as part
13 of your systematic review, did a search
14 and said let me just see if there are
15 case reports out there using other ARBs
16 and developing enteropathy with
17 dechallenge and/or rechallenge? You
18 never did that, did you?

19 MS. SUTTON: Objection to
20 form. Foundation.

21 THE WITNESS: My -- I'm
22 sorry.

23 MS. SUTTON: Go ahead.

24 THE WITNESS: My systematic

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1 review, the search terms were
2 specific to olmesartan.

3 BY MR. PARKER:

4 Q. Well, your systematic review
5 didn't address the question of whether
6 other ARBs have been reported in the
7 literature to be associated with
8 enteropathy based upon dechallenge or
9 rechallenge?

10 MS. SUTTON: Objection.
11 Misstates the report and prior
12 testimony.

13 THE WITNESS: So the
14 information that I used for
15 specificity is I used the MedWatch
16 case reports, FAERS, nonrandomized
17 studies, and the FDA. And you'll
18 see the FDA makes a statement
19 that, according to the FDA, the
20 other seven ARBs do not appear to
21 demonstrate evidence for an
22 ARB-induced spruelike enteropathy.
23 And this is on that tracked safety
24 tissue that we spoke about

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1 previously.

2 And then you'll see from my
3 FAERS analysis, you can look at
4 the -- you can look at the effect
5 estimates in there and see that
6 there's a difference in the
7 magnitude of that effect estimate.
8 And you'll also see that
9 Dr. Hansen says that my assessment
10 of olmesartan versus other ARBs
11 directly, he didn't not do that on
12 his own because he believes that
13 my analysis was accurate, and he
14 would have come up with the same
15 conclusions as me.

16 BY MR. PARKER:

17 Q. Certainly you would
18 conclude -- I mean you would agree that
19 being scientific and doing a systematic
20 review, you would not want to ignore
21 evidence that might be germane to a
22 question, right?

23 A. So I agree with you. But my
24 search strategy was specific to

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1 olmesartan.

2 Q. I understand that. But,
3 Doctor, your search strategy seemed to be
4 designed to avoid coming up with any
5 evidence about other ARBs. Am I
6 mistaken?

7 MS. SUTTON: Objection to
8 form. Foundation. Misstates
9 testimony.

10 THE WITNESS: Because the
11 question is about the relationship
12 between olmesartan and spruelike
13 enteropathy.

14 BY MR. PARKER:

15 Q. What does specificity go to,
16 Doctor?

17 A. So the information that I
18 used for the different elements of the
19 Bradford Hill criteria didn't necessarily
20 have to all come from my systematic
21 review.

22 Q. Well, let's just --

23 A. And it is --

24 Q. I'm sorry.

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1 A. Yes.

2 Q. Now, firstly, Doctor, to
3 achieve a score or a ranking of probable,
4 as we have discussed, requires not only
5 temporality and dechallenge, but also the
6 ability to rule out other explanations of
7 the condition under the WHO scale?

8 A. So cannot be explained by a
9 disease or other drugs, that assessment
10 criteria, is that what you're referring
11 to?

12 Q. Let me be more specific so
13 the record is clear, in fairness. In
14 order to achieve a probable/likely, one
15 of the things you have to satisfy to
16 yourself is that it is unlikely to be
17 attributed to disease or other drugs?

18 A. That is correct.

19 Q. Okay. So when you go to
20 your report, and you wrote, "162 cases
21 has a positive dechallenge suggesting a
22 WHO causality assessment of probable for
23 the majority of cases (temporality and
24 dechallenge)," what you should have said,

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1 plus unlikely to be attributed to the
2 disease or other drugs?

3 A. So because those -- the case
4 reports from the literature are in
5 peer-reviewed journals and reported by
6 clinicians and are labeled
7 olmesartan-induced enteropathy, or as
8 you've seen, spruelike enteropathy, I
9 took that clinician's assessment in the
10 literature that went through the peer
11 review process, that that case in that
12 clinician's assessment was published in
13 that journal because it was
14 olmesartan-induced enteropathy.

15 Thereby, my assumption was
16 that it was unlikely to be attributed to
17 disease or other drugs.

18 Q. Because an author of a case
19 report says, "I got a case of spruelike
20 enteropathy," you just assumed that
21 means -- it meant, because that author
22 claimed it, it was unlikely to be
23 attributed to disease or other drugs? Do
24 I understand your methodology correctly?

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1 MS. SUTTON: Objection to
2 form. Foundation. Misstates her
3 testimony.

4 THE WITNESS: Okay. So
5 every -- so every case report by
6 definition met the criteria for
7 temporality with olmesartan
8 preceding the adverse event. And
9 then 162 of these cases had a
10 positive dechallenge, which, using
11 the WHO causality assessment of
12 probable, so they had temporality
13 plus dechallenge, and because it
14 was in the peer-reviewed
15 literature, I considered that they
16 had sufficient info that they
17 would have ruled out alternative
18 causes and considered these
19 probable cases.

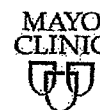
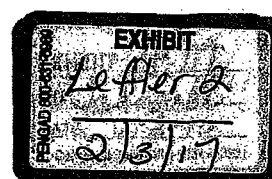
20 BY MR. PARKER:

21 Q. Okay.

22 (Document marked for
23 identification as Exhibit
24 Huftless-43.)

Exhibit C

ORIGINAL ARTICLE



Severe Spruelike Enteropathy Associated With Olmesartan

Alberto Rubio-Tapia, MD; Margot L. Herman, MD; Jonas F. Ludvigsson, MD, PhD; Darlene G. Kelly, MD, PhD; Thomas F. Mangani, MD; Tsung-Teh Wu, MD, PhD; and Joseph A. Murray, MD

Abstract

Objective: To report the response to discontinuation of olmesartan, an angiotensin II receptor antagonist commonly prescribed for treatment of hypertension, in patients with unexplained severe spruelike enteropathy.

Patients and Methods: All 22 patients included in this report were seen at Mayo Clinic in Rochester, Minnesota, between August 1, 2008, and August 1, 2011, for evaluation of unexplained chronic diarrhea and enteropathy while taking olmesartan. Celiac disease was ruled out in all cases. To be included in the study, the patients also had to have clinical improvement after suspension of olmesartan.

Results: The 22 patients (13 women) had a median age of 69.5 years (range, 47-81 years). Most patients were taking 40 mg/d of olmesartan (range, 10-40 mg/d). The clinical presentation was of chronic diarrhea and weight loss (median, 18 kg; range, 2.5-37 kg), which required hospitalization in 14 patients (64%). Intestinal biopsies showed both villous atrophy and variable degrees of mucosal inflammation in 15 patients, and marked subepithelial collagen deposition (collagenous sprue) in 7. Tissue transglutaminase antibodies were not detected. A gluten-free diet was not helpful. Collagenous or lymphocytic gastritis was documented in 7 patients, and microscopic colitis was documented in 5 patients. Clinical response, with a mean weight gain of 12.2 kg, was demonstrated in all cases. Histologic recovery or improvement of the duodenum after discontinuation of olmesartan was confirmed in all 18 patients who underwent follow-up biopsies.

Conclusion: Olmesartan may be associated with a severe form of spruelike enteropathy. Clinical response and histologic recovery are expected after suspension of the drug.

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From the Division of Gastroenterology and Hepatology (A.R.-T., J.F.L., D.G.K., T.F.M., J.A.M.), Department of Internal Medicine (M.L.H.), and Department of Laboratory Medicine and Pathology (T.-T.W.), Mayo Clinic, Rochester, MN; Clinical Epidemiology Unit, Department of Medicine, Karolinska University Hospital and Karolinska Institutet, Stockholm, Sweden (J.F.L.); and Department of Pediatrics, Örebro University Hospital, Örebro, Sweden (J.F.L.).



Olmesartan is one of several angiotensin II receptor antagonists used for management of hypertension since 2002.¹ Diarrhea is a common adverse effect of many medications, although the mechanisms underlying diarrhea remain unclear in most cases. Enteropathy as a cause of drug-induced diarrhea has been reported previously with the use of azathioprine and mycophenolate mofetil.²⁻⁴ We first suspected the possible connection between enteropathy and olmesartan when 2 consecutive patients referred to our institution for evaluation of presumed refractory celiac disease reported unexplained clinical improvement during hospitalization but prompt relapse following hospital discharge. They asked if the disease course could have been due to their hypertensive medications, which were withheld on hospitalization because of hypotension. At the same time, we were studying a cohort of patients with collagenous sprue and discovered olmesartan use in one-third of the patients with a recent diagnosis of the disorder.⁵ As additional patients were identified with similar clinical features (eg, chronic diarrhea, weight loss, unexplained spruelike enteropathy with or without abnormal subepithelial collagen deposition, negative

celiac serology, and lack of response to gluten exclusion), a perceived association between these features and olmesartan evolved. It also became clear that these patients were unlikely to have celiac disease, as all lacked IgA tissue transglutaminase antibodies and had never responded to a gluten-free diet. The clinical observation of improvement of gastrointestinal symptoms and subsequent demonstration of histologic recovery after olmesartan withdrawal prompted us to advise our patients with unexplained spruelike enteropathy to discontinue olmesartan. We reported our observation to US Food and Drug Administration officials and submitted reports using the MedWatch system.

In this article, we describe the clinical manifestations in 22 patients with unexplained spruelike enteropathy that improved clinically after discontinuation of olmesartan.

PATIENTS AND METHODS

This study was approved by the Mayo Clinic Institutional Review Board. Patients were considered for inclusion in the study if they had chronic diarrhea (>4 weeks) while taking olmesartan and met 2 additional criteria. First, the cause of their enteropathy

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could not be established after a systematic diagnostic evaluation that included investigation for disorders associated with nonresponsive celiac disease as previously reported by our group.⁶ Second, they had to improve clinically after discontinuation of olmesartan. Most of these patients had undergone extensive evaluation by their referring physicians and had had several therapeutic trials, without benefit. The electronic medical records of 24 such patients seen at Mayo Clinic in Rochester, Minnesota, between August 1, 2008, and August 1, 2011, were reviewed by one physician (M.L.H.). Two of the 24 patients were excluded from the study, 1 who had tropical sprue and 1 who improved clinically and histologically with oral budesonide before suspension of olmesartan.

Data Abstraction

Clinical and laboratory data were abstracted from the medical record. Only data that reflected conditions that existed before suspension of olmesartan were included as baseline data. We defined categories of body weight using body mass index and World Health Organization criteria.⁷ Anemia was defined in women as a hemoglobin level of less than 12 g/dL (to convert to g/L, multiply by 10) and in men as a hemoglobin level of less than 13.5 g/dL. Hypoalbuminemia was defined as an albumin value lower than 3.5 g/dL (to convert to g/L, multiply by 10). HLA-DQ typing,⁸ celiac disease serology (tissue transglutaminase antibodies or deamidated gliadin peptide antibodies by enzyme-linked immunosorbent assay and endomysial antibodies on monkey esophagus by indirect immunofluorescence),⁹⁻¹¹ and assessment of response to a gluten-free diet were investigated. Anti-enterocyte antibodies were tested using primate intestine by indirect immunofluorescence and were performed at The Children's Hospital of Philadelphia, as reported by Akram et al.¹² Severe enteropathy was defined by the presence of at least one of the following criteria: (1) need for hospitalization because of severe dehydration, electrolyte imbalance, and/or acute renal failure, (2) need for total parenteral nutrition, and (3) weight loss of more than 10 kg.

Histopathology

Pathology material (biopsy samples from the gastrointestinal tract) was reviewed by one of the authors (T.-T.W.). The number of intraepithelial lymphocytes per 100 epithelial cells, degree of villous atrophy graded with the modified Marsh classification,¹³ presence of subepithelial collagen, degree of lamina propria inflammation, and presence of acute inflammation were assessed. The presence of aberrant or clonal intraepithelial lymphocytes was inves-

tigated by CD3 and CD8 immunostaining¹⁴ and polymerase chain reaction,¹⁵ respectively. When multiple small bowel biopsies were performed as part of the diagnostic evaluation and before withdrawal of the drug, the baseline biopsy was considered to be the small bowel biopsy performed closest to the date of suspension of olmesartan. Follow-up biopsies were defined as biopsies performed at least 30 days after the date of suspension of olmesartan. Other disorders of the gastrointestinal tract (when present) were diagnosed using accepted pathologic criteria (eg, microscopic colitis).¹⁶

Outcomes After Suspension of Olmesartan

Clinical response was defined as the resolution of diarrhea. Weight gain was considered a positive finding. *Remission* required both a clinical response and confirmation by normal findings on intestinal biopsy during follow-up. All patients who had been on a gluten-free diet were followed up after reintroduction of gluten and withdrawal of corticosteroids.

Medication Use

We reviewed the medication history of all patients, including the duration of treatment, dosage, and response of diarrhea to a trial of olmesartan withdrawal. Alternative antihypertensive drugs used after suspension of olmesartan are reported.

Statistical Analyses

Data were summarized using descriptive statistics, including total numbers and percentages for categorical variables and median or mean (range) for continuous variables.

RESULTS

The 22 patients (13 women) had a median age of 69.5 years (range, 47-81 years). Twenty-one of the patients were non-Hispanic white, and 1 patient was black. Patients were residents of 16 different US states (Table 1).

The most frequent clinical diagnoses at time of referral were nonresponsive/refractory celiac disease (n=10) and unexplained sprue (n=6). Most patients were taking 40 mg/d of olmesartan (range, 10-40 mg/d) for several months or years before the onset of diarrhea. Detailed information about the duration of exposure to olmesartan before onset of diarrhea was available in the medical record in 14 patients (64%). Among these, the mean duration was 3.1 years (range, 0.5-7 years). An additional 5 patients were taking olmesartan for at least 1 year before the onset of symptoms. Information about duration of exposure to olmesartan before onset of diarrhea was not available in 3 patients.

TABLE 1. Demographic Characteristics, Outcome, and Alternative Antihypertensive Drugs Used After Suspension of Olmesartan in 21 Patients With Sprue-Like Enteropathy

Patient No./sex/age (y)	Weight loss (kg)	Outcome after suspension of olmesartan*	Alternative antihypertensive drug
1/F/59	14	Remission	Metoprolol
2/F/62	11	Clinical response	None
3/F/72	31	Remission, weight gain (13.3 kg)	Bisoprostol-hydrochlorothiazide
4/M/66 ^b	18	Remission, weight gain (11 kg)	Metoprolol
5/M/81	2.5	Remission, weight loss (4.1 kg)	Lisinopril, metoprolol
6/M/64	14	Clinical response	Amlodipine
7/F/65	11	Remission, weight gain (4.2 kg)	Amlodipine, hydrochlorothiazide
8/M/76	12	Remission, weight gain (13.4 kg)	Amlodipine, hydrochlorothiazide
9/M/64	20.5	Remission, weight gain (15.7 kg)	Amlodipine, hydrochlorothiazide
10/F/72	30	Remission, weight gain (28 kg)	Amlodipine, atenolol, hydrochlorothiazide
11/M/74	15	Clinical response	Hydrochlorothiazide
12/M/58	57	Remission, weight gain (23.4 kg)	Amlodipine, metoprolol
13/F/77	29	Remission, weight gain (9.7 kg)	Atenolol, hydrochlorothiazide
14/F/76	7	Remission, weight gain (2.9 kg)	Hydrochlorothiazide
15/M/68	18	Remission, weight gain (14.9 kg)	Metoprolol
16/F/71	9	Remission, weight gain (11.9 kg)	Triamterene, hydrochlorothiazide
17/F/66 ^b	20.5	Clinical response, weight gain (13.4 kg)	Spironolactone, carvedilol
18/F/64 ^c	50	Clinical response, weight gain (4 kg)	Amlodipine
19/F/75	41	Remission	None
20/M/47	32	Remission, weight gain (13.9 kg)	Metoprolol, amlodipine, doxazosin
21/F/71	18	Remission, weight gain (10.2 kg)	Atenolol, hydralazine
22/F/74	40	Remission, weight gain (6.3 kg)	None

*Weight change (defined by weight at diagnosis minus weight at last follow-up visit) is provided when available in the medical record.

^bCase previously published.⁵

^cNon-Hispanic black.

Clinical Manifestations

Diarrhea had been present for a median of 19.2 months (range, 3-53 months) before suspension of the drug. At the time of presentation, all patients had diarrhea and weight loss (median weight loss, 18 kg; range, 2.5-57 kg). Nausea and vomiting were present in 15 patients (68%), abdominal pain in 11 (50%), bloating in 9 (41%), and fatigue in 15 (68%). The onset of diarrhea was sudden in 9 patients. The stool frequency was extremely abnormal, with a median of 6 evacuations per day (range, 3-42 evacuations per day). Among 8 patients with timed stool collection, the mean stool weight was 933.1 g/24 h (range, 225-3225 g/24 h), and mean fecal fat was 28.3 g/24 h (range, 8-50 g/24 h). Although timed stool weight was not investigated in all patients, 14 patients (64%) required hospitalization because of severe dehydration (4 patients had acute renal failure). Total parenteral nutrition was necessary in 4 patients. At the time of the first visit at Mayo Clinic, 11 of the patients had normal weight, 6 were under-

weight, 4 were overweight, and 1 was obese. All but one patient (patient 16) met criteria for severe enteropathy.

Laboratory Findings

Results of IgA tissue transglutaminase antibody testing were negative in all patients. IgA endomysial antibody results were negative in all 9 patients who underwent testing. HLA-DQ typing was performed in 21 patients: DQ2 was present in 15 patients, DQ8 in 2 patients, and neither DQ2 nor DQ8 in 4 patients. Anti-enterocyte antibody testing was done in 19 patients (86%), and results were negative in 16 (including 7 patients who had a positive nonspecific nuclear pattern of unknown clinical significance) and positive with a linear/apical pattern in 3.

Fourteen patients (64%) had normocytic normochromic anemia (2 had elevated red blood cell distribution width suggesting anisocytosis); the lowest hemoglobin level was 9.3 g/dL. Ten patients (45%) had hypoalbuminemia; the lowest albumin

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level was 2 g/dL. Twelve patients (55%) had one (n=3) or multiple (n=9) electrolyte abnormalities. Zinc deficiency was documented in 7 patients.

Small bowel bacterial overgrowth was confirmed by culture of duodenal aspirate ($>10^5$ colony-forming units per milliliter) in 12 patients at some point during clinical evolution. A trial of oral antibiotics was used in 10 patients without clinical benefit (rifaximin in 5, tetracycline in 3, ciprofloxacin in 1, and ciprofloxacin-metronidazole in 1). An additional 2 patients received no therapy for small bowel bacterial overgrowth.

Histologic Findings

In all patients, baseline intestinal biopsies demonstrated villous atrophy with variable degrees of mucosal inflammation (Table 2). Total villous atrophy was observed in 15 patients and partial villous atrophy in 7 patients. A thick band of subepithelial collagen deposition (collagenous sprue) was seen in 7 patients (2 cases had been reported previously⁵). Active/acute inflammation was observed in 15 patients, and increased intraepithelial lymphocytes were found in 14 patients. Aberrant (or clonal) intraepithelial lymphocytes were not detected among the 12 patients tested.

Colonoscopy with random colonic biopsies was performed in 13 patients (59%). Microscopic colitis was found in 5 patients (2 had lymphocytic colitis and 3 had collagenous colitis).

Biopsies of the stomach were available in 14 patients (64%). Lymphocytic gastritis was diagnosed in 5 patients and collagenous gastritis in 2 patients. Chronic gastritis was diagnosed in an additional 7 patients (1 had *Helicobacter pylori* infection).

Treatment and Subsequent Course

Most of the patients in our study had undergone several therapeutic trials, without apparent clinical benefit, before referral to Mayo Clinic, including the use of a gluten-free diet for months (n=20), systemic corticosteroids and/or budesonide (n=20), opioid-derived antidiarrheal agents (most often loperamide) (n=10), pancreatic enzymes (n=4), bile acid sequestrant (n=4), metronidazole (n=4), azathioprine (n=3), and octreotide (n=3).

Clinical response was observed in all 22 patients after suspension of olmesartan. Besides tapering of corticosteroids, no medication was needed to control diarrhea after clinical response was achieved with suspension of the drug. Patients following a gluten-free diet were advised to abandon the diet immediately if they lacked the celiac susceptibility genotypes or to gradually reintroduce gluten if they were HLA-DQ2 or DQ8 positive. No patient had recurrence of symptoms after restarting a gluten-

containing diet. Follow-up body weight after suspension of olmesartan was available in 17 patients; 16 had weight gain, with a mean weight gain of 12.2 kg (range, 2.9–28 kg), and 1 patient (patient 5) who had edema at diagnosis lost 4.1 kg during follow-up despite clinical remission.

At the time of this report, follow-up intestinal biopsies have been performed in 18 patients (82%) after a mean of 242.3 days (range, 54–707 days) from the date of suspension of olmesartan. Histologic recovery of the duodenum was documented in 17 patients (Figure). Focal partial villous atrophy was observed in 1 case (patient 2) on a follow-up duodenal biopsy obtained 54 days after suspension of olmesartan. Follow-up gastric biopsies were performed at the same time as repeated biopsy of the duodenum in 5 of the 7 patients with either lymphocytic or collagenous gastritis (no gastric biopsy results were available for patient 11). Follow-up gastric biopsies showed normal mucosa in 4 patients and nonspecific mild chronic gastritis in 2 patients (patients 20 and 22). Follow-up colonoscopies with biopsies of the colon were not performed in the 5 patients with microscopic colitis.

DISCUSSION

We describe a group of patients with unexplained severe spruelike enteropathy while taking olmesartan. We also provide evidence of both clinical and histologic improvement after suspension of olmesartan. Celiac disease was excluded by conventional methods of serology and the absence of clinical response to a gluten-free diet.¹⁷ Other less common enteropathies were excluded (Table 3).

We acknowledge that this case series lacks all the information necessary to prove causality but rather reflects an association. No deliberate challenge test with olmesartan was undertaken because of the life-threatening nature of the syndrome, although 2 patients reported anecdotally that their symptoms had worsened when they restarted olmesartan before the potential association was recognized, and 2 patients experienced improvement when olmesartan was stopped when they were hospitalized (for dehydration and hypotension) and worsened in the weeks following discharge and reintroduction of olmesartan. Resolution of the presenting symptoms and subsequent histologic improvement after suspension of olmesartan, in the absence of clinical evidence of other diseases associated with enteropathy, suggest that the association is not likely to be due to chance.

Pathologic findings in the duodenal biopsy can mimic celiac disease or collagenous sprue. Clinicopathologic correlation is advised to confirm the diagnosis of olmesartan-associated enteropathy. Pathologic evidence of involvement of other organs (eg, the

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Baseline duodenal biopsy results									
Patient No.	Villous atrophy	IELs (/100 epithelial cells) ^a	Acute/active inflammation	Thickened collagen band	Absent cells/clones ^b	Outcome follow-up: duodenal biopsy results	Time d ^c	Other GI findings ^e	
1	Total	Normal	Yes	No	No/No	Normal	404	Lymphocytic gastritis (HP negative, immunostain)	Collagenous colitis
2	Total	80-100	Yes	Yes	No/NA	Improvement, focal partial villous atrophy	54	Chronic gastritis (HP negative, immunostain)	Normal
3	Total	Normal	Yes	No	No/No	Normal	231	NA	Collagenous colitis
4	Total	40	Yes	Yes	No/No	Normal	263	Collagenous gastritis	NA
5	Total	>100	Yes	No	NA/NA	Normal	54	NA	Normal
6	Partial	60	Yes	No	NA/NA	NA	NA	NA	NA
7	Partial	>100	No	No	No/No	Normal	159	NA	Normal
8	Total	40-60	Yes	No	NA/NA	Normal	143	Lymphocytic gastritis (HP negative, immunostain)	Normal
9	Total	60-80	Yes	No	No/No	Normal	188	NA	NA
10	Partial	Normal	No	No	No/No	Normal	404	NA	NA
11	Partial	50	Yes	No	No/No	NA	NA	Mild lymphocytic gastritis (HP negative, immunostain)	NA
12	Partial	Normal	Yes	No	No/No	Normal, focal active duodenitis	116	Mild active chronic gastritis (HP negative, immunostain)	Mild active chronic colitis
13	Total	40	Yes	Yes	NA/NA	Normal	171	Active chronic gastritis (HP negative, immunostain)	NA
14	Partial	60-80	No	No	NA/NA	Normal	240	Mild active chronic gastritis (HP negative, immunostain)	NA
15	Total	Normal	No	Yes	NA/NA	Normal	181	Mild chronic gastritis (HP negative, no immunostain)	Normal
16	Total	Normal	No	Yes	No/No	Normal	607	Collagenous gastritis	Collagenous colitis
17	Total	40-60	Yes	Yes	No/No	NA	NA	Mild chronic gastritis (HP negative, no immunostain)	Focal acute colitis
18	Partial	Normal	No (marked eosinophilia)	No	NA/NA	NA	NA	NA	NA
19	Total	30	Yes	No	NA/NA	Normal	76	Severe active chronic gastritis and ulceration (HP negative, immunostain)	NA
20	Total	Normal	No	Yes	No/No	Normal	707	Lymphocytic gastritis (HP positive)	Lymphocytic colitis
21	Total	80-100	Yes	No	NA/NA	Normal	179	NA	Lymphocytic colitis
22	Total	80	Yes	No	NA/NA	Normal	184	Lymphocytic gastritis (HP negative, immunostain)	Normal

^aHP = Helicobacter pylori; IELs = intraepithelial lymphocytes; NA = not available.

^bNormal <25/100 epithelial cells.

^cAbsent cells defined by >50% CD3⁺/CD8⁺ IELs on immunostaining; clone defined by T-cell receptor gene clonal rearrangement by polymerase chain reaction.

^dTime from suspension of omeprazole to follow-up biopsy.

^eAny time before suspension of omeprazole.

OLMESARTAN AND ENTEROPATHY



stomach and colon) suggests that this disorder may affect the entire gastrointestinal tract. We provide evidence of resolution of inflammation and/or fibrosis in the stomach and duodenum after suspension of olmesartan, implying that these changes are associated with the use of olmesartan. Even though follow-up colonoscopies were not performed in the 5 patients with documented microscopic colitis, clinical remission was achieved in all of these patients, a very unlikely outcome in the presence of persistent inflammation or fibrosis of the colon. Recovery of duodenal mucosa in a relatively short time (median of 8 months from suspension of olmesartan to follow-up biopsies) is a relevant clinical observation because mucosal recovery in other small bowel disorders, such as celiac disease, may take years to occur despite adherence to a gluten-free diet, especially in older adults.^{18,19}

Finding small bowel bacterial overgrowth in 12 patients is intriguing and consistent with prior observations of association of small bowel bacterial overgrowth and enteropathy in symptomatic patients with celiac disease.^{20,21} The reason for this association is unknown. Thus, although small bowel bacterial overgrowth is a well-recognized cause of chronic diarrhea in the right clinical setting,²² in this series, the lack of clinical response to oral antibiotics suggests that gastrointestinal symptoms are not explained by the effects of an increased number of bacteria in the small bowel.

The mechanisms underlying olmesartan-associated enteropathy are unknown. The long delay between onset of olmesartan therapy and the development of diarrhea (and enteropathy) suggests cell-mediated immunity damage rather than type I hypersensitivity. Recently, angiotensin receptor blockers have been suggested to have inhibitory effects on transforming growth factor β action.^{23,24} Transforming growth factor β is crucially important in the maintenance of gut immune homeostasis.^{25,26} Olmesartan is an orally administered prodrug (olmesartan medoxomil) that is rapidly metabolized to the active component (olmesartan) by esterases in the gastrointestinal mucosa, portal blood, and liver.²⁷ Nevertheless, the possible role of transforming growth factor β inhibition in olmesartan-associated enteropathy is a question that requires investigation. We do not know if other angiotensin II receptor blockers can be associated with a similar form of enteropathy, but active investigation for similar cases among patients using other drugs of the same class is under way. All our patients with olmesartan-associated enteropathy received antihypertensive drugs from a different class after suspension of olmesartan. HLA-DQ2 was present in 68% of patients with olmesartan-associated enteropathy, a prevalence higher than the 25% to 30% expected for the general population,^{28,29} suggesting that perhaps

Gastrointestinal symptoms (eg, chronic diarrhea, weight loss, steatorrhea)
Negative IgA tissue transglutaminase antibodies (or endomysial antibodies)
Evidence of enteropathy (villous atrophy) with or without collagen deposition or intraepithelial lymphocytosis
Lack of clinical response to gluten exclusion
Exclusion of other causes of enteropathy (eg, celiac disease)
Evidence of clinical and histologic improvement after suspension of olmesartan

the presence of HLA-DQ2 may increase the risk of immune-mediated damage in these patients. This may be another example of drug-associated enteropathy of which the medical community should be aware and could result in the identification of several more cases.

CONCLUSION

We report a unique case series to support a novel association between severe spruelike enteropathy and olmesartan. Physicians who encounter patients with diarrheal syndromes should consider medications as a cause, although the potential role for olmesartan had not been considered in these patients by any of the physicians prescribing the medications or treating the diarrheal illness.

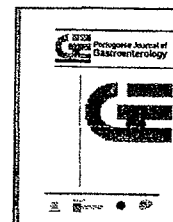
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Correspondence: Address to Joseph A. Murray, MD, Division of Gastroenterology and Hepatology, Mayo Clinic, 200 First St SW, Rochester, MN 55905 (murray.joseph@mayo.edu).

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Exhibit D



EDITORIAL

Sprue-Like Enteropathy Associated With Olmesartan: A New Kid on the Enteropathy Block

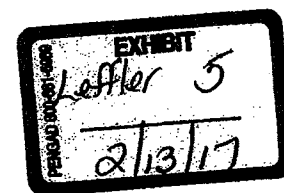


Enteropatia Tipo *Sprue* Induzida Por Olmesartan: Uma Nova Entidade no Campo Das Enteropatias

Isabel A. Hujoel^a, Alberto Rubio-Tapia^{a,b,*}

^a Department of Internal Medicine, Mayo Clinic, Rochester, MN, USA

^b Division of Gastroenterology and Hepatology, Mayo Clinic, Rochester, MN, USA



Sprue-like enteropathy associated with olmesartan, first identified by our group in 2012,¹ is characterized by chronic diarrhea (often severe) and weight loss that is unresponsive to a gluten-free diet. Laboratory work-up commonly reveals non-specific anemia, hypoalbuminemia, electrolyte imbalance, and vitamin deficiencies, consistent with a severe malabsorption process. Histopathological findings include a combination of duodenal villous atrophy, increased intraepithelial lymphocytes, and a thickened subepithelial collagen layer (collagenous sprue). Histologic changes can be limited to the small bowel, or may include the entire gastrointestinal tract, with findings such as lymphocytic/collagenous gastritis and colitis. Individuals with sprue-like enteropathy associated with olmesartan have negative celiac serology. The majority may have either HLA-DQ2 or DQ8 haplotypes (61–81%).¹ Diagnosis of olmesartan associated enteropathy should therefore be considered in cases of villous atrophy with negative celiac serology (so-called seronegative villous atrophy). Confirmation of diagnosis requires clinical resolution of symptoms after olmesartan withdrawal. Mucosal recovery is also expected within 3–6 months of olmesartan withdrawal and a follow-up duodenal biopsy is reasonable.

Severe sprue-like enteropathy associated with olmesartan appears to be rare although a spectrum of disease severity may be possible.² The annual incidence rate of enteropathy in a French population-based study among patients treated with olmesartan for at least 6 months was calculated at 1.3 cases per 1000 individuals per year (95% confidence interval (CI) of 0.5–2.6).³ This rate is not significantly different from the rate of 0.63 cases of incident celiac disease per 1000 reported by the Mini-Sentinel (95% CI: .38–.99) ($p=0.16$).⁴ The Mini-Sentinel reported that rates of incident celiac disease were of similar magnitude for all angiotensin receptor blockers with, for instance, a rate of 0.43 cases per 1000 (95% CI: 0.33–0.55) for losartan. Mini-Sentinel data therefore suggest that enteropathy may be a class-related drug effect. Such a hypothesis is supported by sporadic case-reports of enteropathy possibly associated with irbesartan,⁵ losartan,⁶ and valsartan.⁷ However, a nation-wide case-control Swedish study failed to show any association between the use of either angiotensin converting enzyme blockers or non-olmesartan angiotensin receptor blockers and subsequent villous atrophy.⁸ Thus, there is clear predominance of published data relating olmesartan to enteropathy (Table 1).

Sprue-like enteropathy associated with olmesartan should be ruled out early in the investigation of patients with seronegative villous atrophy. Indeed, a case-series on 72 patients with seronegative villous atrophy found the most frequent etiologies to be seronegative CD (28%), medication-related (26%), unclassified sprue (14%), autoimmune enteropathy (4%), and giardia (4%).¹³ Of the

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* Corresponding author.

E-mail address: rubiotapia.alberto@mayo.edu (A. Rubio-Tapia).

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Table 1 Case-reports and case-series of sprue-like enteropathy associated with olmesartan published after the Mayo Clinic 2012 original case-series.

Reference number	Author	Country	Date of Publication	Number of cases	Comments
9	Talbot	USA	2012	1	Follow up histology: no
10	Dreifuss et al.	USA	2013	1	Follow up histology: no
11	Nielsen et al.	USA	2013	1	Follow up histology: yes Time after cessation: 3 months Resolution of histologic changes: yes
12	Stanich et al.	USA	2013	1	Follow up histology: no
13	DeGaetani et al.	USA	2013	16	Follow up histology: 2/16 Time after cessation: 12 months Resolution of histologic changes: yes (2/2)
14	Abdelghany et al.	USA	2014	1	Follow up histology: no
15	Tran et al.	USA	2014	1	Follow up histology: no
16	Théophile et al.	France	2014	5	Follow up histology: yes (2/5), no (3/5) Time after cessation: 2 months (2/2) Resolution of histologic changes: yes (1/2), partial (1/2); IELs still present but VA resolved
17	Gaur et al.	USA	2014	1	Follow up histology: no
18	Fiorucci et al.	Italy	2014	1	Follow up histology: no
19	Khan et al.	USA	2014	1	Follow up histology: no
20	Hartranft et al.	USA	2014	1	Follow up histology: no
21	Ianiro et al.	Italy	2014	3	Follow up histology: 3/3 Time after cessation: 3 months (2/3), not reported (1/3) Resolution of histologic changes: yes 2/3, partial (1/3)
22	Gallivan et al.	Australia	2014	1	Follow up histology: yes Time after cessation: 4 months Resolution of histologic changes: yes
5	Marthey et al.	France	2014	36	Follow up histology: 15/36 Time after cessation: 9 months Resolution of histologic changes: yes (15/15)
23	Scialom et al.	France	2015	7	Follow up histology: 5/7 Time after cessation: 2-7 months Resolution of histologic changes: yes (4/5); one had biopsy while on anti-TNF-antibodies and olmesartan discontinued with resolution of histologic changes (1/5)
24	Kulaj et al.	Canada	2015	1	Follow up histology: yes Time after cessation: 14 weeks Resolution of histologic changes: yes
25	Muñoz- Muñoz et al.	Spain	2015	1	Follow up histology: no
26	Marco-Marqués et al.	Spain	2015	11	Follow up histology: no
27	Heerasing et al.	Australia	2015	1	Follow up histology: yes Time after cessation: 4 months Resolution of histologic changes: yes
28	Fabian et al.	Austria	2015	1	Follow up histology: yes Time after cessation: 2 months Resolution of histologic changes: yes
29	Fukushima et al.	Japan	2016	1	Follow up histology: yes Time after cessation: 11 months Resolution of histologic changes: yes
30	Imperatore et al.	Italy	2016	1	Follow up histology: yes Time after cessation: 8 months Resolution of histologic changes: yes
31	Schiepatti et al.	Italy	2016	2	Follow up histology: Yes (2/2) Time after cessation: 2 months (2/2) Resolution of histologic changes: yes (2/2)
3	Esteve et al.	Spain	2016	20	Follow up histology: yes (19/20) Time after cessation: 3-12 months Resolution of histologic changes: yes (18/19), no (1/19)

medication-related seronegative villous atrophy, roughly 84% were attributed to olmesartan.¹³ Early identification of individuals with sprue-like enteropathy associated with olmesartan is clinically relevant as symptoms can be severe and/or life-threatening with expected clinical response within days of olmesartan withdrawal.¹

In this issue of *GE Portuguese Journal of Gastroenterology*, case reports by da Silva et al.³², Carneiro et al.³³ and Eusébio et al.³⁴, highlight the importance of considering sprue-like enteropathy associated with olmesartan when approaching a patient with seronegative villous atrophy and

provide further information to aid in diagnosis of this emergent disease.

In their case-report, da Silva et al. outline a practical algorithm to approach diagnosis of seronegative villous atrophy that does not respond to a gluten free diet.³² The first proposed step following testing for celiac serology is a review of the patient's medication list. In the four cases reported in this issue, symptoms resolved within 48 h to one week of discontinuation of olmesartan.³²⁻³⁴ Trialing a patient off of a medication early on in the evaluation of seronegative villous atrophy could therefore provide both a rapid

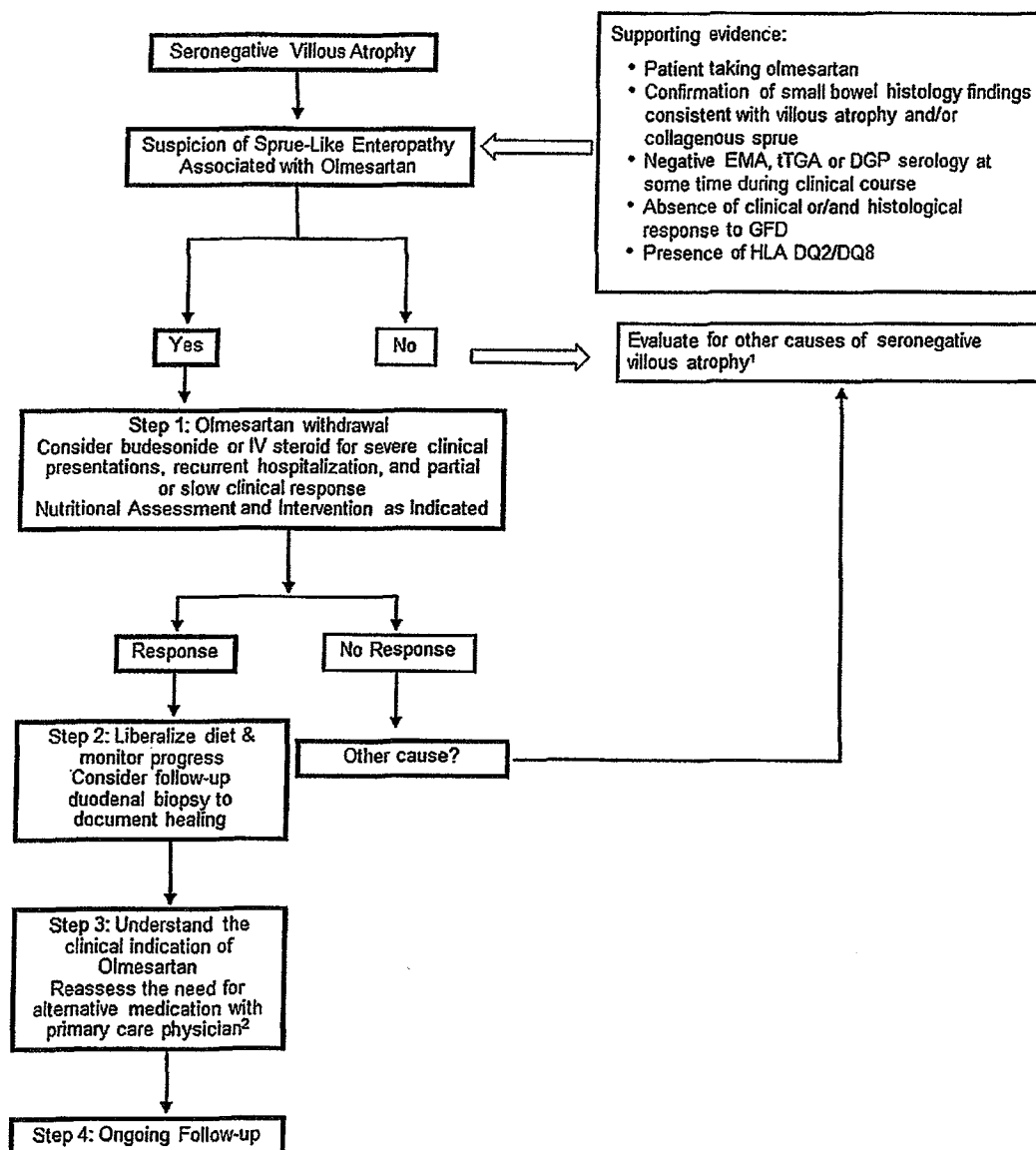


Figure 1 Proposed Management for Patients with Sprue-like Enteropathy associated with Olmesartan. 1. Differential diagnosis includes (but it is not limited to) seronegative celiac disease, other drug-related enteropathies, autoimmune enteropathy, tropical sprue, small-bowel bacterial overgrowth, hypogammaglobulinemic sprue, Giardiasis, refractory celiac disease, Whipple's disease, collagenous sprue, and unclassified sprue. 2. If there is a need for continuation of alternative therapy, we recommend to use a different class of medication whenever is clinically possible.

and cost-effective diagnosis. It is our practice that following olmesartan withdrawal, we try to understand the primary indication for olmesartan therapy and reassess the need for alternative medications together with the patient's primary care physician. It has been our experience that a considerable number of patients do not need any medications after suspension of olmesartan.

Eusébio et al.³⁴ identify a unique finding of elevated transaminases in a case of olmesartan associated enteropathy. They propose that this may be due to the same mechanism behind the hypertransaminasemia seen in CD.

Carneiro et al.³³ report on a case diagnosed with systemic sclerosis during the work-up for sprue-like enteropathy associated with olmesartan. The association with autoimmune diseases has been reported in several other studies.^{3,5,23} In line with this observation, there are reports of individuals with sprue-like enteropathy associated with olmesartan responding to immunosuppressive treatment.^{5,23} Our open-label experience suggests that some patients with severe symptoms, recurrent hospitalizations due to dehydration or both slow and/or partial response to olmesartan withdrawal may have some benefit from a short course of steroids such as budesonide (Fig. 1).

The association between autoimmune diseases and olmesartan associated enteropathy is consistent with the emerging evidence supporting an immune-based pathophysiology. One recent study by our group looking at duodenal biopsies of those taking olmesartan versus those who had discontinued the medication showed an increased CD8+ cells, FoxP3+ cells, and IL15R in biopsies of those taking olmesartan, similar to what is seen in CD.³⁵ In addition, we demonstrated an increased IL15 expression and disruption of tight junction proteins (ZO-1) in olmesartan-treated Caco-2 cells.³⁵ This suggests that olmesartan may trigger a similar change in intestinal epithelial cells as gluten does in those with CD although further study of the underlying mechanisms would be needed to fully understand the pathophysiology of sprue-like enteropathy associated with olmesartan, the new kid on the enteropathy block.

Conflict of interest

The authors declare no conflicts of interest.

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Exhibit E

13166
Protected Information - Steven M. Lagana, M.D.

1 IN THE UNITED STATES DISTRICT COURT
2 FOR THE DISTRICT OF NEW JERSEY

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6 IN RE: BENICAR : MDL NO. 2606
7 (OLMESARTAN) PRODUCTS :
8 LIABILITY LITIGATION :
9 :

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February 7, 2017

PROTECTED INFORMATION

Oral expert deposition of
STEPHEN M. LAGANA, M.D., taken pursuant
to notice, was held at the law offices of
Robins Kaplan LLP, 601 Lexington Avenue,
Suite 3400, New York, New York, beginning
at 10:09 a.m., on the above date, before
Kimberly A. Cahill, a Federally Approved
Registered Merit Reporter and Notary
Public.

GOLKOW TECHNOLOGIES, INC.
877.370.3377 ph | 917.591.5672 fax
deps@golkow.com

Protected Information - Steven M. Lagana, M.D.

1 APPEARANCES:

2

MAZIE SLATER KATZ & FREEMAN, LLC
3 BY: ADAM M. SLATER, ESQUIRE
103 Eisenhower Parkway, 2nd Floor
4 Roseland, New Jersey 07068
(973) 228-9898
5 aslater@mskf.net
Representing the Plaintiffs

6

7 VENABLE LLP

BY: BRUCE R. PARKER, ESQUIRE

8 750 East Pratt Street

Suite 900

9 Baltimore, Maryland 21202

(410) 244-7534

10 brparker@Venable.com

Representing Daiichi Sankyo, Inc.

11

12 DRINKER BIDDLE & REATH, LLP

BY: JESSICA L. BRENNAN, ESQUIRE

13 600 Campus Drive

Florham Park, New Jersey 07932

14 (973) 549-7000

jessica.brennan@dbr.com

15 Representing Daiichi Sankyo, Inc.

16

17 ALSO PRESENT:

18 Amy Klug, Esquire

Assistant General Counsel

19 Daiichi Sankyo, Inc.

20

21

22 - - -

23

24

Protected Information - Steven M. Lagana, M.D.

1 - - -
2 I N D E X
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4
5 Testimony of: STEPHEN M. LAGANA, M.D.
6 By Mr. Parker 8
By Mr. Slater 394

7
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9 E X H I B I T S
10 - - -

11	NO.	DESCRIPTION	PAGE
12			
13	Lagana-1	Notice of	8
14		Deposition of	
15		Stephen M. Lagana,	
16		M.D.	
17	Lagana-2	Packet of Bills	8
18		from Dr. Lagana,	
19		Beginning with	
20		"Bill 9 - General"	
21	Lagana-3	Rule 26 Expert	53
22		Report of Stephen	
23		Lagana, M.D.	
24		Regarding General	
		Causation	
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		(Olmesartan)	
		Products Liability	
		Litigation	
		Supplemental	
		Reliance List for	

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1 himself has come to the deposition
2 room and said this patient has
3 never touched olmesartan before
4 this developed and then started
5 taking olmesartan after that? Is
6 that the situation that you're
7 describing?

8 MR. PARKER: Well, I didn't
9 invoke God, but I'll make the
10 question easier for you.

11 BY MR. PARKER:

12 Q. Is someone is diagnosed with
13 unclassified sprue who has never taken --
14 and let's just say his doctors say so and
15 patients say so -- never taken
16 olmesartan, they can continue to have
17 unclassified sprue notwithstanding the
18 fact that they're now taking olmesartan.

19 A. I think that's a possible,
20 although quite rare, scenario, but I do
21 concede that that is a possible scenario.
22 I would also just add to that, we don't
23 know in those patients if olmesartan
24 could contribute or make -- or exacerbate

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1 their sprue. For instance, we don't know
2 in -- there are patients who have -- just
3 based on epidemiology, there are
4 certainly patients who have true celiac
5 disease and who have been prescribed
6 olmesartan. We don't know if the
7 olmesartan affects those patients
8 differently than patients without celiac
9 disease.

10 Q. And there's no literature to
11 suggest that it does.

12 MR. SLATER: Objection.
13 You can answer.

14 THE WITNESS: Or doesn't.

15 MR. PARKER: Let's talk
16 about the affirmative. Nobody's
17 published a paper of any type
18 positing or proposing that a
19 patient with celiac disease is
20 made worse if they start on
21 olmesartan.

22 MR. SLATER: Objection.
23 You can answer.

24 THE WITNESS: There's

Protected Information - Steven M. Lagana, M.D.

1 nothing in the published
2 literature to that effect yet.

3 BY MR. PARKER:

4 Q. Now, going back to my
5 question about unclassified sprue, it is
6 reported in the literature that patients
7 who have unclassified sprue, some number
8 of them spontaneously resolve.

9 Have you seen that in the
10 literature?

11 A. That sounds familiar, but
12 before I agree to that point, I'd like to
13 -- if you have something with you that
14 documents that, I'd like to confirm that.

15 Q. Sure, sure.

16 Have you ever seen that in
17 your clinical practice, of patients with
18 diagnosed unclassified sprue resolving
19 spontaneously, or has it been reported to
20 you by your colleagues in the GI section?

21 A. And for the purposes of this
22 question, we're excluding the cases seen
23 at Columbia who were thought to be
24 unclassified and later categorized as

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1 olmesartan?

2 Q. Yes, I'm not involving
3 olmesartan at all.

4 A. Okay. I don't remember a
5 case, but I don't think it sounds
6 unreasonable.

7 - - -

8 (Deposition Exhibit No.
9 Lagana-6, 2016 Original Article
10 "The clinical and phenotypical
11 assessment of seronegative villous
12 atrophy; a prospective UK centre
13 experience evaluating 200 adult
14 cases over a 15-year period
15 (2000-2015)" by Aziz, et al, was
16 marked for identification.)

17 - - -

18 BY MR. PARKER:

19 Q. Doctor, Exhibit 6 is a copy
20 of the study by Drs. Aziz and others,
21 which your colleague, Peter Green, is a
22 co-author on.

23 Do you see that?

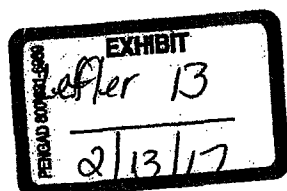
24 A. Yep.

Exhibit F

ORIGINAL ARTICLE

The clinical and phenotypical assessment of seronegative villous atrophy; a prospective UK centre experience evaluating 200 adult cases over a 15-year period (2000–2015)

Imran Aziz,^{1,2} Mohammad F Peerally,¹ Jodie-Hannah Barnes,^{1,2} Vigneswaran Kandasamy,^{1,2} Jack C Whiteley,^{1,2} David Partridge,³ Patricia Vergani,⁴ Simon S Cross,^{2,4} Peter H Green,⁵ David S Sanders^{1,2}



► Additional material is published online only. To view please visit the journal online (<http://dx.doi.org/10.1136/gutjnl-2016-312271>).

¹Academic Department of Gastroenterology, Royal Hallamshire Hospital, Sheffield, UK

²University of Sheffield, Sheffield, UK

³Department of Microbiology, Royal Hallamshire Hospital, Sheffield, UK

⁴Department of Histopathology, Royal Hallamshire Hospital, Sheffield, UK

⁵Department of Medicine, Columbia University College of Physicians and Surgeons, Celiac Disease Center, New York, New York, USA

Correspondence to

Dr Imran Aziz, Academic Department of Gastroenterology, Royal Hallamshire Hospital, Sheffield Teaching Hospitals, Sheffield S10 2JF, UK; imran.aziz@sth.nhs.uk

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ABSTRACT

Background Seronegative villous atrophy (SNVA) is commonly attributed to coeliac disease (CD). However, there are other causes of SNVA. More recently angiotensin-2-receptor-blockers (A2RBs) have been reported as an association but data on SNVA have been limited to centres evaluating complex case referrals and not SNVA in general.

Objectives To provide clinical outcomes and associations in a large prospective study overseeing all newcomers with SNVA.

Design Over a 15-year period (2000–2015) we evaluated 200 adult patients with SNVA at a UK centre. A diagnosis of either seronegative CD (SNCD) or seronegative non-CD (SN-non-CD) was reached. Baseline comparisons were made between the groups, with 343 seropositive CD subjects serving as controls.

Results Of the 200 SNVA cases, SNCD represented 31% (n=62) and SN-non-CD 69% (n=138). The human leucocyte antigen (HLA)-DQ2 and/or DQ8 genotype was present in 61%, with a 51% positive predictive value for SNCD. The breakdown of identifiable causes in the SN-non-CD group comprised infections (27%, n=54), inflammatory/immune-mediated disorders (17.5%, n=35) and drugs (6.5%, n=13; two cases related to A2RBs). However, no cause was found in 18% (n=36) and of these 72% (n=26/36) spontaneously normalised duodenal histology while consuming a gluten-enriched diet. Following multivariable logistic regression analysis an independent factor associated with SN-non-CD was non-white ethnicity (OR 10.8, 95% CI 2.2 to 52.8); in fact, 66% of non-whites had GI infections. On immunohistochemistry all groups stained positive for CD8-T-cytotoxic intraepithelial lymphocytes. However, additional CD4-T helper intraepithelial lymphocytes were occasionally seen in SN-non-CD mimicking the changes associated with refractory CD.

Conclusions Most patients with SNVA do not have CD, in particular those who are not white. Furthermore, a subgroup with no obvious aetiology will show spontaneous histological resolution while consuming gluten. These findings suggest caution in empirically prescribing a gluten-free diet without investigation.

INTRODUCTION

Coeliac disease (CD) affects 0.7–1% of the population and can be defined as a state of heightened

Significance of this study

What is already known on this subject?

- Seronegative villous atrophy (SNVA) is a diagnostic and therapeutic dilemma.
- The causes of SNVA are vast but can be broadly grouped into seronegative coeliac disease (SNCD) and seronegative non-coeliac disease (SN-non-CD).
- To date no study has systematically evaluated all newcomers with SNVA.

What are the new findings?

- SNCD accounts for 31% of SNVA cases, with the remaining 69% due to SN-non-CD.
- A positive human leucocyte antigen DQ2 and/or DQ8 status is seen in 61% of SNVA cases; its positive predictive value for SNCD is roughly 51%.
- An independent risk factor associated with SN-non-CD is non-white ethnicity, suggestive of infective aetiology.
- Overall, almost one in five patients with SNVA will have no identifiable cause; reassuringly, the majority of these will spontaneously normalise duodenal histology despite undertaking a gluten challenge.

How might it impact on clinical practice in the foreseeable future?

- Individuals with SNVA should not be prescribed a gluten-free diet prior to further investigations. This is because of the wide differential diagnoses and that a subgroup with no obvious aetiology spontaneously normalises its duodenal histology while maintaining gluten intake.

immune response to ingested gluten in genetically susceptible individuals.^{1–3} All patients with CD carry the human leucocyte antigen (HLA)-DQ2 and/or DQ8 genotypes, although these alleles are also present in approximately 40% of the general population.³ A cast-iron diagnosis of CD can be made on the basis of demonstrating duodenal

Coeliac disease

villous atrophy in the presence of serum IgA endomysial and/or tissue transglutaminase antibodies.^{4–6} This mode of presentation may be termed seropositive CD (SPCD) and following a systematic review accounts for approximately 93% of cases with villous atrophy,⁷ although some international groups have reported a lower prevalence (table 1).^{8–15}

With this in regard, diagnostic and therapeutic dilemmas occur when villous atrophy is found in the context of negative coeliac serology.^{8–15} This clinical entity is termed seronegative villous atrophy (SNVA), the causes of which can be broadly grouped into CD or non-CD related.^{16–17} The reasons for seronegative CD (SNCD) include patients who have reduced gluten intake prior to investigations,¹⁸ lesser degrees of villous atrophy,¹³ selective IgA deficiency,¹⁹ immunosuppressive therapy or those with long-standing advanced CD within the spectrum of ulcerative jejunitis/enteropathy associated T cell lymphoma.¹⁵ The causes of seronegative non-CD (SN-non-CD) are vast ranging from infective, inflammatory, immune-mediated and drug-related.^{16–17} Such examples include autoimmune enteropathy,²⁰ bacterial overgrowth,¹⁶ common variable immunodeficiency,²¹ Crohn's disease,²² gastroenteritis,²³ giardiasis,^{24–25} graft versus host disease,²⁶ HIV enteropathy,²⁷ mycobacterium tuberculosis,^{25–28} peptic duodenitis ± *H. pylori*,^{17–29–32} radiation enteritis,³³ tropical sprue^{25–34} and Whipple's disease.³⁵ Medications include non-steroidal anti-inflammatory drugs,^{36–38} azathioprine,³⁹ methotrexate,⁴⁰ mycophenolate mofetil⁴¹ and, most recently, angiotensin-2-receptor-blockers (A2RBs), in particular olmesartan.^{16–42–45} Finally, in some instances no unifying cause can be found and such patients are classified as idiopathic/unclassified sprue, the natural history of which is unknown.^{16–17}

Studies attempting to evaluate diagnostic outcomes in SNVA have thus far been limited to a US centre overseeing complex case referrals from a wide catchment area.¹⁶ In such circumstances a high prevalence of SNCD and olmesartan-related enteropathy has been reported, the latter accounting for a striking 22% of SNVA cases.¹⁶ However, we hypothesise that this may not be reflective of SNVA as seen in routine GI practice. Furthermore, the clinical and histological phenotype of SNCD and SN-non-CD has not been established, nor how these entities contrast to the more conventionally seen SPCD. Such an evaluation may prove useful in understanding the spectrum of villous atrophy while also aiding clinicians towards the correct diagnosis when posed with the challenges of SNVA.

In light of this, the aim of our study was to provide a large comprehensive overview of all patients with SNVA seen at a UK centre over a 15-year period. Furthermore, we sought to identify differences between SNCD and SN-non-CD, using SPCD as controls.

MATERIAL AND METHODS

Setting

This study was carried out between the time periods of 2000 and 2015 at the Royal Hallamshire Hospital, Sheffield, South Yorkshire, UK. The hospital is located in northern England and provides a secondary/tertiary-care service to a population of 500 000 people. The unit undertakes approximately 6000 oesophago-gastro-duodenoscopies per year.

Participants

Over the 15-year period we prospectively recruited 200 consecutive adult patients presenting with SNVA. The identification of SNVA was based upon duodenal biopsies showing villous atrophy yet with negative serum IgA endomysial and tissue transglutaminase antibodies from the outset.

As for our control group we recruited 343 patients with SPCD diagnosed within the same department between the years 2005 and 2011.

Histology

Throughout the study period the gastroenterology department had a policy of taking four duodenal biopsy specimens from the second part of the duodenum in those with suspected malabsorption. All duodenal biopsy specimens were fixed in buffered formalin and embedded in paraffin wax. Standard 3 µm thick sections at three levels were stained with H&E. The duodenal biopsies were routinely reported by one of a team of seven GI histopathologists. Agreement was then performed by one of two expert GI histopathologists reviewing SNVA biopsy samples (coauthors SSC and PV). Intraepithelial lymphocytosis was defined as >25 per 100 enterocytes. Villous atrophy was identified according to the Marsh-Oberhuber criteria, using the most severe lesion present: Marsh 3a (partial villous atrophy, PVA); Marsh 3b (subtotal villous atrophy, SVA); or Marsh 3c (total villous atrophy, TVA).^{46–47}

The groups were also assessed for differences in immunohistochemistry based on CD3 pan-lymphocyte marker and specific CD8-T cytotoxic and CD4-T helper intraepithelial lymphocyte expression.

Coeliac serology

The initial panel of coeliac serology testing was IgA based, with endomysial antibodies detected by immunofluorescence on primate oesophagus sections from The Binding Site (Birmingham, UK). IgA tissue transglutaminase antibodies were assayed by using ELISA kits (Aesku Diagnostics, Wendelsheim, Germany), with titres less than or equal to 15 U/mL taken as negative. Of note, our immunology department does not automatically test for immunoglobulin or total IgA levels when

Table 1 Studies where coeliac serology have shown low sensitivities in villous atrophy.

First author	Year	Country	No of villous atrophy cases	Positive coeliac serology, n (%)	Negative coeliac serology, n (%)
Rostami ⁸	1999	Netherlands	69	42 (61%)	27 (39%)
Dickey ⁹	2000	Northern Ireland	89	69 (78%)	20 (22%)
Dahle ¹⁰	2001	Scotland	53	42 (79%)	11 (21%)
Dahle ¹¹	2001	Scotland	114	92 (81%)–99 (87%)	15 (11%)–22 (19%)
Clemente ¹²	2002	Italy	111	95 (86%)	16 (14%)
Abrams ¹³	2004	USA	115	74 (64%)	41 (36%)
Collin ¹⁴	2005	European multicentre	126	112 (89%)–118 (94%)	8 (6%)–14 (11%)
Salmi ¹⁵	2006	Finland	177	151 (85%)	26 (15%)

Coeliac serology as defined by endomysial and/or tissue transglutaminase antibodies.

processing coeliac serology. Rather, these have to be specifically requested as does IgG coeliac serology.

Baseline characteristics

We collected baseline characteristic data on the SNVA and SPCD cohorts. Taking into consideration the potential aetiologies and clinical manifestations this included age, gender, ethnicity, city residence, clinical symptoms, past medical history, current medication, grading of villous atrophy, HLA-DQ2/8 status, as well as laboratory parameters in the form of haemoglobin, ferritin, folate, vitamin B₁₂, albumin, calcium, erythrocyte sedimentation rate and/or C reactive protein.

All the data (other than age) were inputted as categorical. This included converting numerical laboratory values into either within the normal or abnormal range, thereby overcoming the difficulties that arise over a 15-year period with departmental changes in testing kits and reference values.

Diagnostic workup for SNVA

All patients with SNVA were investigated in line with a systematic protocol, similar to that proposed by other expert groups, aiming to diagnose either SNCD or SN-non-CD (figure 1).^{16 17} It is important to bear in mind that, despite several international guidelines on CD, there is no consensus on how to approach subjects with SNVA.⁴⁻⁶ Some physicians may suggest a trial of a

gluten-free diet (GFD) followed by clinical and histological reassessment.⁴⁻⁶ However, this can be fraught with uncertainty given that up to 32% of patients with SN-non-CD report favourable clinical response to a GFD.¹⁷ Furthermore, mucosal recovery in adult CD is slow with histological abnormalities often persisting beyond 2-5 years and in some cases never normalising.⁴⁸⁻⁵⁰ Therefore, adopting such an approach in SNVA could potentially lead to unnecessary delays given the wide differential diagnoses. Hence, patients with SNVA in our study were asked to continue a gluten-containing diet until investigations were complete and a firm diagnosis reached. This approach is also useful in that it allows progression of villous atrophy and detectable serum antibodies in some cases of SNCD.⁵¹

Mortality

At the end of December 2015 mortality rates were calculated. Overall survival was calculated in years and defined as the time from diagnosis to death. Surviving patients were censored at the time of last follow-up.

Statistics

Statistical analysis was carried out using SPSS V21.0 software (SPSS, Chicago, USA), with significance set at a p value of <0.05. A complete-case analysis approach was adopted to

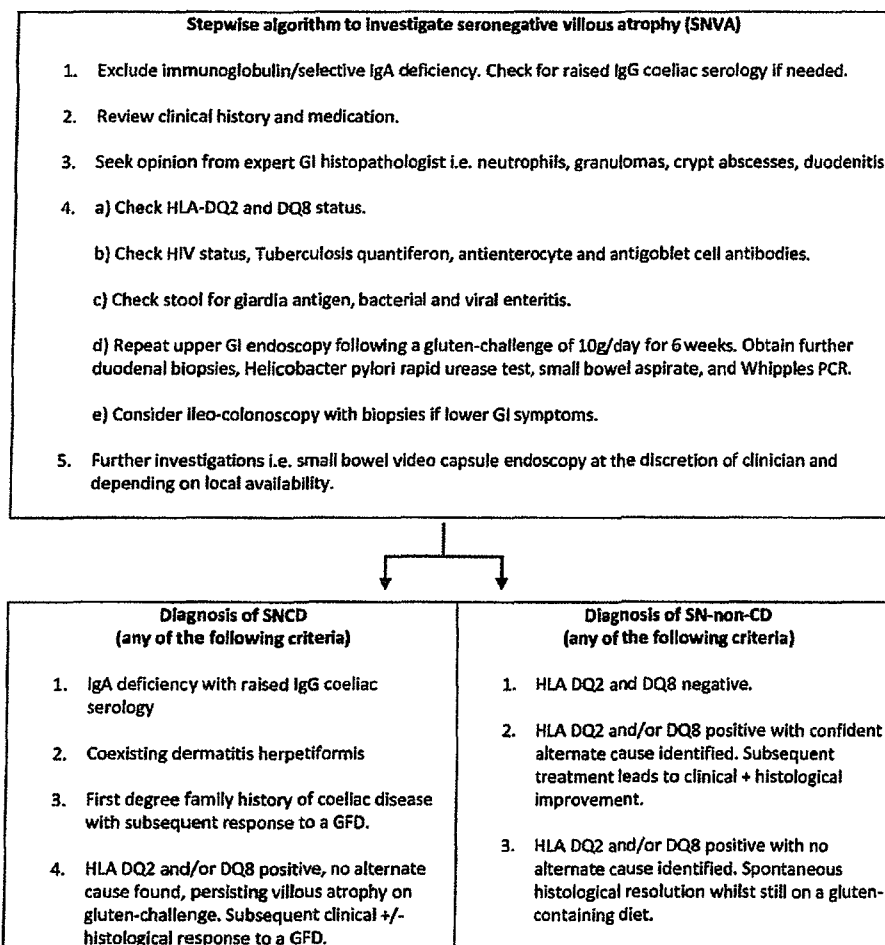


Figure 1 Stepwise proposed algorithm used to investigate and diagnose causes of seronegative villous atrophy (SNVA). GFD, gluten-free diet; HLA, human leucocyte antigen; SNCD, seronegative coeliac disease; SN-non-CD, seronegative non-coeliac disease.

Celiac disease

address the limited data which were missing completely at random. Categorical variables were summarised by descriptive statistics, including total numbers and percentages, with comparisons between groups performed using the χ^2 test or Fisher's exact test. Normally distributed continuous variables were summarised by mean and SD with comparisons between groups performed using the unpaired Student's t-test. We performed dichotomous logistic regression between the SNCD and SN-non-CD groups using a forward stepwise method with a

p value of <0.1 for entry into the analysis with all variables available for inclusion into the model. Finally, overall survival was analysed using Kaplan-Meier curves and significance compared using the log-rank test.

RESULTS**Characteristics of SNVA**

The baseline characteristics of the 200 patients with SNVA are provided in table 2. The patient cohort comprised 83%

Table 2 Baseline characteristics of SNVA subjects and SPCD controls

	Total SNVA (n=200)	SN-non-CD (n=138; 69%)	SNCD (n=62; 31%)	p Value (between SNCD and SN-non-CD)	SPCD controls (n=343)	p Value (SPCD controls vs SN-non-CD)	p Value (SPCD controls vs SNCD)
Demographics							
Mean age \pm SD	51.2 \pm 17.6	51.4 \pm 17.3	50.9 \pm 18.2	0.89	43.5 \pm 17.3	<0.001	0.002
Female, n	127 (63.5%)	84 (60.9%)	43 (69.4%)	0.25	242 (70.6%)	0.04	0.85
White ethnicity, n	165 (82.5%)	105 (76.1%)	60 (96.8%)	<0.001	307 (89.5%)	<0.001	0.1
Sheffield city resident, n	166 (83%)	116 (84%)	50 (80.6%)	0.55	343 (100%)	<0.001	<0.001
Clinical symptoms							
Diarrhoea, n	120 (60%)	84 (61%)	36 (58.1%)	0.71	153 (44.6%)	0.001	0.05
Weight loss, n	71 (35.5%)	52 (37.7%)	19 (30.6%)	0.34	40 (11.7%)	<0.001	<0.001
Abdominal pain, n	98 (49%)	69 (50%)	29 (46.8%)	0.67	121 (35.3%)	0.003	0.08
Bloating, n	62 (31%)	43 (31.2%)	19 (30.6%)	0.94	102 (29.7%)	0.76	0.89
Dyspepsia, n	28 (14%)	24 (17.4%)	4 (6.5%)	0.04	19 (5.5%)	<0.001	0.79
Reflux, n	32 (16%)	24 (17.4%)	8 (12.9%)	0.42	27 (7.9%)	0.002	0.19
Nausea, n	39 (19.5%)	27 (19.6%)	12 (19.4%)	0.97	52 (15.2%)	<0.001	0.001
Constipation, n	32 (16%)	24 (17.4%)	8 (12.9%)	0.42	52 (15.2%)	0.54	0.65
Fatigue, n	32 (16%)	19 (13.8%)	13 (21%)	0.2	91 (26.5%)	0.003	0.36
Past medical history							
Autoimmunity, n	37 (18.5%)	18 (13%)	19 (30.6%)	0.003	72 (21%)	0.04	0.09
Family history of CD, n	7 (3.5%)	0 (0%)	7 (11.2%)	<0.001	55 (16%)	<0.001	0.34
Recent gastroenteritis-type history, n	23 (11.5%)	18 (13%)	5 (8.1%)	0.31	8 (2.3%)	<0.001	0.03
Crohn's disease, n	1 (0.5%)	1 (0.7%)	0 (0%)	0.5	1 (0.3%)	0.49	1.0
Lymphoproliferative disorders, n	4 (2%)	3 (2.2%)	1 (1.6%)	1.0	2 (0.6%)	0.15	0.39
HIV, n	2 (1%)	2 (1.4%)	0 (0%)	1.0	1 (0.3%)	0.2	1.0
Tuberculosis, n	2 (1%)	2 (1.4%)	0 (0%)	1.0	1 (0.3%)	0.2	1.0
Medication							
A2RB, n	8 (4%)	6 (4.3%)	2 (3.2%)	1.0	8 (2.3%)	0.23	0.66
Aspirin, n	29 (14.5%)	21 (15.2%)	8 (12.9%)	0.67	29 (8.5%)	0.03	0.26
NSAIDs, n	19 (9.5%)	16 (11.6%)	3 (4.8%)	0.13	11 (3.2%)	<0.001	0.46
Methotrexate, n	2 (1%)	1 (0.7%)	1 (1.6%)	0.5	2 (0.6%)	1.0	0.39
Mycophenolate, n	1 (0.5%)	1 (0.7%)	0 (0%)	1.0	1 (0.3%)	0.49	1.0
Azathioprine, n	0 (0%)	0 (0%)	0 (0%)	–	3 (0.9%)	0.56	1.0
Bloods							
Anaemia, n	61/198 (30.8%)	43/137 (31.4%)	18/61 (29.5%)	0.79	154/343 (44.9%)	0.007	0.03
Low ferritin, n	75/190 (39.5%)	51/130 (39.2%)	24/60 (40%)	0.92	207/333 (62.2%)	<0.001	0.001
Low folate, n	35/192 (18.3%)	28/131 (21.4%)	7/61 (11.5%)	0.1	100/333 (30%)	0.06	0.003
Low vitamin B ₁₂ , n	31/193 (16.1%)	21/131 (16%)	10/62 (16.1%)	0.99	61/331 (18.4%)	0.54	0.67
Low calcium, n	22/186 (11.8%)	17/126 (13.5%)	5/60 (8.3%)	0.31	28/332 (8.4%)	0.1	0.98
Low albumin, n	21/198 (10.6%)	19/137 (13.9%)	2/61 (3.3%)	0.03	16/336 (4.8%)	0.001	1.0
Raised ESR and/or CRP, n	51/192 (26.6%)	40/132 (30.3%)	11/60 (18.3%)	0.08	82/324 (25.3%)	0.28	0.25
HLA-DQ2 and/or DQ8 positive, n	118/193 (61%)	58/133 (43.6%)	60/60 (100%)	<0.001	112/112 (100%)	<0.001	1.0
Duodenal histology							
Intraepithelial lymphocytosis, n	177 (88.5%)	116 (84%)	61 (98.4%)	0.003	343 (100%)	<0.001	0.15
Crypt hyperplasia, n	177 (89%)	117 (84.8%)	61 (98.4%)	0.003	343 (100%)	<0.001	0.15
Partial villous atrophy, n	159 (79.5%)	120 (87%)	39 (62.9%)		82 (23.9%)		
Subtotal villous atrophy, n	25 (12.5%)	10 (7.2%)	15 (24.2%)	<0.001	144 (42%)	<0.001	<0.001
Total villous atrophy, n	16 (8%)	8 (5.8%)	8 (12.9%)		117 (34.1%)		

Bold values are statistically significant.

A2RB, angiotensin-2-receptor-blocker; CD, coeliac disease; CRP, C reactive protein; ESR, erythrocyte sedimentation rate; HLA, human leucocyte antigen; NSAIDs, non-steroidal anti-inflammatory drugs; SNCD, seronegative coeliac disease; SN-non-CD, seronegative non-coeliac disease; SNVA, seronegative villous atrophy; SPCD, seropositive coeliac disease.

(n=166) who were residents of Sheffield and thus classed as secondary-care referrals. There were 17% (n=34) who were referred from another city for a tertiary-care opinion. The mean age was 51.2 years, with 63.5% (n=127) female and 82.5% (n=165) of white ethnicity.

The most frequently reported clinical symptoms were diarrhoea (60%, n=120), abdominal pain (49%, n=98), weight loss (35.5%, n=71) and bloating (31%, n=62). Autoimmunity was present in 18.5% (n=37) of cases, with 3.5% (n=7) also having a family history of CD. A recent history suggestive of gastroenteritis was elicited in 11.5% (n=23) of cases. The use of A2RBs was seen in 4% (n=8), of which 7 were on candesartan and 1 was on irbesartan; no patient was taking olmesartan.

Blood tests revealed anaemia in 30.8%, with associated haematinic deficiencies ranging from 16.1% to 39.5%. A raised erythrocyte sedimentation rate and/or C reactive protein was present in 26.6% of patients. The presence of positive HLA-DQ2 and/or DQ8 was seen in 61.1% (n=118/193).

Finally, histological grading of duodenal biopsies showed intraepithelial lymphocytosis in 88.5% (n=177), with the majority of patients found to have PVA at 79.5% (n=159). In contrast, SVA was seen in 12.5% (n=25) and TVA in 8% (n=16).

Aetiology of SNVA

Following systematic evaluation of 200 SNVA cases, we diagnosed SNCD in 31% (n=62) of cases with the remaining 69% (n=138) due to SN-non-CD. The breakdown of all causes is shown in figure 2.

In the 62 cases identified as having SNCD, 14 were diagnosed with relative ease based on (1) selective IgA deficiency but with raised IgG coeliac serology (n=9, three also had associated first degree family history of CD), (2) first degree family history of CD alone with subsequent response to a GFD (n=4) and (3) dermatitis herpetiformis (n=1). The other 48 patients were diagnosed with SNCD on the basis of having positive HLA-DQ2 and/or DQ8 status, no alternate cause found, persisting villous atrophy following a gluten rechallenge, with subsequent clinical±histological response to a GFD.

A wide range of aetiologies was established in the 138 SN-non-CD cases, commonly infective, medication-induced and

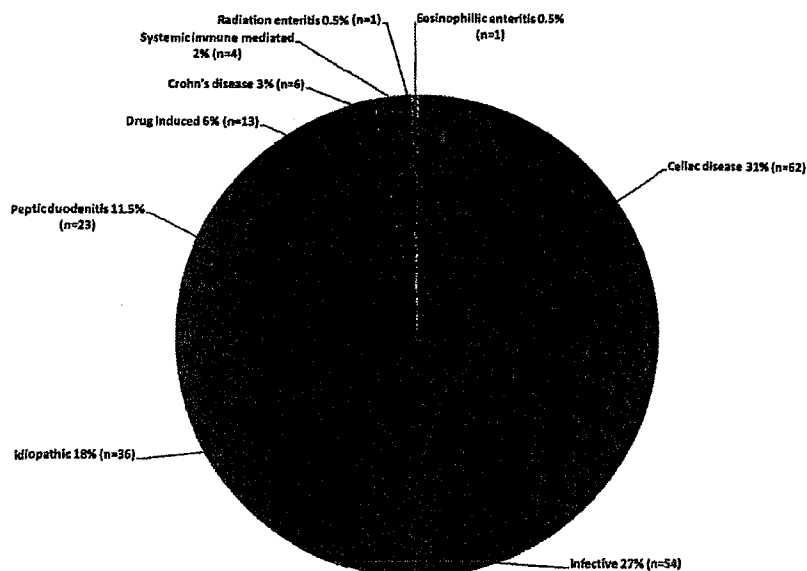
inflammatory in nature. In total, there were 54 cases attributed to an infection. This included *Helicobacter pylori* induced duodenitis alone (n=21) or in conjunction with *Mycobacterium tuberculosis* (n=2), *Mycobacterium avium* intracellulare (n=1) and HIV (n=1). Other causes included viral gastroenteritis based upon clinical history (n=7), giardiasis (n=6), small bowel bacterial overgrowth (n=4), HIV enteropathy (n=2), ascariasis (n=2), *Mycobacterium tuberculosis* (n=2), tropical sprue (n=2), *Campylobacter* (n=1), candidiasis (n=1), Whipple's disease (n=1) and *Mycobacterium avium* intracellulare (n=1). There were 13 cases which occurred as a result of medication; 9 due to non-steroidal anti-inflammatory drug-related duodenitis, and the others were a case each related to methotrexate, mycophenolate mofetil, irbesartan and a possible association with candesartan. There were 23 cases of non-specific peptic duodenitis, 6 cases of Crohn's disease and 4 cases due to systemic immune-mediated disorders which included a case each of sarcoidosis, graft versus host disease, autoimmune enteropathy and common variable immunodeficiency. There was a case each of radiation enteritis and eosinophilic enteritis. Following appropriate treatment these showed clinical and histological improvement.

Finally, in 36 cases of SN-non-CD, despite extensive investigations, we were unable to elicit any cause and these patients were labelled as idiopathic/unclassified sprue. Interestingly, 72% (n=26/36, 11 of whom were HLA-DQ2/8 positive) had spontaneously normalised their duodenal biopsies when rechallenged with gluten, suggesting transient villous atrophy. This was seen on average 9 months after the index biopsy had shown villous atrophy. Of the remaining 10 cases, all HLA-DQ2/8 negative, 4 required immunosuppressive therapy for persisting unexplained villous atrophy with the other 6 either lost to follow-up or refusing further endoscopic investigations given their clinical stability.

Risk factors for diagnostic outcomes

Univariate analysis comparing the SNVA subgroups and SPCD controls are shown in table 2. In summary, the SNVA cohort was older at the time of presentation and more likely to present with symptoms of diarrhoea, abdominal pain, nausea and weight loss.

Figure 2 Causes of seronegative villous atrophy (SNVA) at a UK centre (n=200).



Coeliac disease

In contrast, subjects with SPCD or SNCD were more likely than SN-non-CD to have autoimmunity, family history, and HLA-DQ positivity; however, the positive predictive value of HLA-DQ2/8 for SNCD in the context of SNVA was only 51% (n=60/118). There was also a significant trend towards lesser degrees of villous atrophy from SPCD towards SNCD and then SN-non-CD.

Factors significantly associated with SN-non-CD included non-white ethnicity, dyspepsia, negative HLA-DQ status, lack of intraepithelial lymphocytosis/crypt hyperplasia and hypoalbuminaemia. Multivariable logistic regression analysis of the SNVA cohort showed that an independent factor associated with a diagnosis of SN-non-CD was non-white ethnicity (OR 10.8, 95% CI 2.2 to 52.8, p=0.003). Indeed, 23 of the 35 (66%) non-white subjects presenting with SNVA had a GI infection,

commonly *H. pylori* induced duodenitis; table 3. Only 2 of 35 (5.7%) non-whites with SNVA had SNCD compared with 60 of 165 (36%) whites.

Immunophenotyping of intraepithelial lymphocytes

Immunohistochemistry was performed in 19 SNVA cases of which 14 were SN-non-CD and 5 SNCD. Both groups showed CD8-positive T cytotoxic intraepithelial lymphocytes, similar to that seen in SPCD controls. However, four cases of SN-non-CD also contained CD4-positive T helper cells among the intraepithelial lymphocytes; these cells are associated with refractory CD within the context of CD but in other contexts, such as GI infection, they are a normal component of the immune response (see figure 3 and online supplementary figure S1).

Table 3 Characteristics and diagnostic outcomes in non-whites with SNVA seen at a UK centre

Case	Age/sex	Ethnicity	Symptoms	Marsh grading	HLA-DQ2/8 status	Aetiology of SNVA
1	28/female	Pakistan	Abdominal pain, reflux, weight loss	PVA	+	<i>H. pylori</i> induced duodenitis
2	29/male	Oman	Diarrhoea, nausea, bloating, dyspepsia	PVA	+	No cause found—SNVA resolved
3	30/female	Tunisia	Diarrhoea, anaemia, bloating	PVA	+	Giardiasis
4	33/male	Ghana	Diarrhoea, weight loss, abdominal pain, cough	PVA	+	Sarcoidosis
5	39/male	Somalia	Diarrhoea, bloating, abdominal pain	PVA	+	Small intestinal bacterial overgrowth
6	43/male	Iran	Nausea, dyspepsia, cough, weight loss	PVA	+	Tuberculosis
7	49/female	Pakistan	Anaemia, abdominal pain, bloating, reflux, fatigue, constipation	PVA	+	Small intestinal bacterial overgrowth
8	49/female	India	Anaemia	PVA	+	<i>H. pylori</i> induced duodenitis
9	49/female	Somalia	Diarrhoea, bloating, abdominal pain, anaemia	PVA	+	No cause found—SNVA resolved
10	58/female	India	Abdominal pain, dyspepsia, bloating	PVA	+	No cause found—SNVA resolved
11	65/female	Iraq	Abdominal pain, bloating, dyspepsia, anaemia	PVA	+	Whipple's disease
12	82/female	Yemen	Abdominal pain, bloating, reflux	PVA	+	Peptic duodenitis
13	18/male	Pakistan	Anaemia	SVA	+	Coeliac disease. Associated Sjogren's and IgA deficiency
14	31/female	Pakistan	Diarrhoea, anaemia, nausea, bloating	SVA	+	Mycobacterium avium, <i>H. pylori</i> induced duodenitis
15	53/female	India	Anaemia	SVA	+	NSAIDs
16	71/male	Bangladesh	Anaemia, dyspepsia, bloating	SVA	+	<i>H. pylori</i> induced duodenitis
17	30/male	Iran	Dyspepsia, reflux, weight loss	SVA	+	Coeliac disease
18	22/female	Pakistan	Abdominal pain, nausea, fatigue	PVA	—	<i>H. pylori</i> induced duodenitis
19	26/female	Yemen	Anaemia, weight loss, abdominal pain, nausea, bloating, fatigue	PVA	—	<i>H. pylori</i> induced duodenitis
20	35/female	Caribbean	Diarrhoea, bloating, abdominal pain	PVA	—	<i>H. pylori</i> induced duodenitis
21	36/male	Iraq	Diarrhoea, abdominal pain, bloating	PVA	—	NSAIDs
22	38/male	Zambia	Anaemia, abdominal pain	PVA	—	Tuberculosis, <i>H. pylori</i> induced duodenitis
23	38/female	Bangladesh	Diarrhoea, anaemia, abdominal pain, fatigue	PVA	—	<i>H. pylori</i> induced duodenitis
24	45/female	Pakistan	Anaemia	PVA	—	<i>H. pylori</i> induced duodenitis
25	47/female	Vietnam	Dyspepsia	PVA	—	No cause found—lost to follow-up
26	47/male	Pakistan	Abdominal pain, weight loss, bloating, reflux	PVA	—	Peptic duodenitis
27	47/female	Pakistan	Diarrhoea, bloating	PVA	—	Ascariasis
28	49/female	Bangladesh	Diarrhoea, anaemia, fatigue, fevers, night sweats	PVA	—	Tuberculosis
29	50/male	Caribbean	Diarrhoea, abdominal pain, reflux	PVA	—	<i>H. pylori</i> induced duodenitis
30	51/female	Yemen	Abdominal pain, weight loss	PVA	—	<i>H. pylori</i> induced duodenitis
31	54/female	Bangladesh	Diarrhoea, weight loss, abdominal pain, dyspepsia, fatigue, constipation	PVA	—	No cause found—SNVA resolved
32	75/female	Hong Kong	Diarrhoea, weight loss, anaemia	PVA	—	Small intestinal bacterial overgrowth
33	35/male	Bangladesh	Reflux, dyspepsia, weight loss	SVA	—	<i>H. pylori</i> induced duodenitis
34	57/male	Yemen	Diarrhoea, weight loss	PVA	Not stated	<i>H. pylori</i> induced duodenitis
35	25/male	Caribbean	Diarrhoea	SVA	Not stated	HIV enteropathy, <i>H. pylori</i> induced duodenitis

HLA, human leucocyte antigen; NSAIDs, non-steroidal anti-inflammatory drugs; PVA, partial villous atrophy; SNVA, seronegative villous atrophy; SVA, subtotal villous atrophy.

Coeliac disease

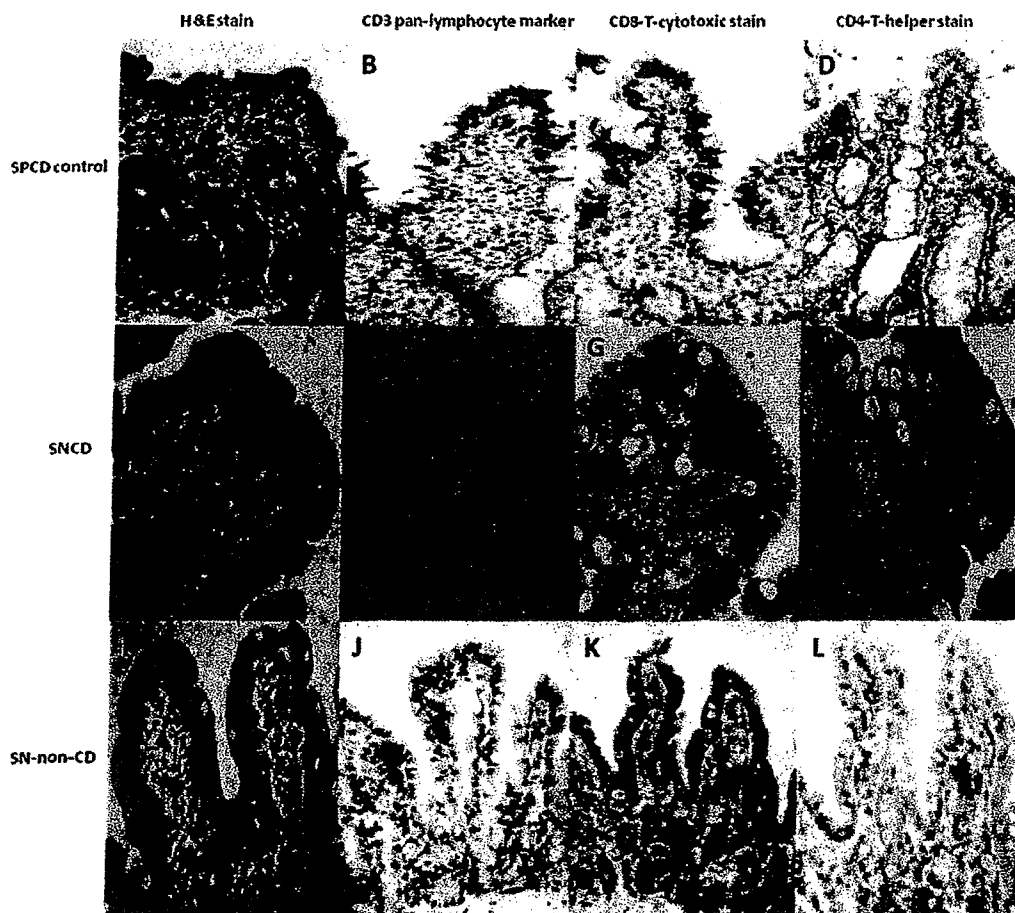


Figure 3 Plates A to D: SPCD control. A white female presenting with anaemia and positive serum IgA endomysial antibody. Duodenal biopsy demonstrated subtotal villous atrophy when stained with haematoxylin and eosin (H&E). It can also be seen that there is an increased number of intra-epithelial lymphocytes stained by the pan-lymphocyte marker CD3. Furthermore, staining of antibodies against different intraepithelial lymphocyte phenotype revealed that they are all of the CD8-T-cytotoxic stain and not CD4-T-helper cells. This is the classical pattern of coeliac disease. Plates E to H: SNCD patient. A white female presenting with diarrhoea. Serum IgA endomysial antibodies were negative but duodenal biopsy showed subtotal villous atrophy. There were increased intraepithelial lymphocytes noted following CD3 pan-lymphocyte stain, which on immunophenotypic differentiation revealed CD8-T-cytotoxic cells but not CD4-T-helper cells. Her HLA-DQ2 was positive, no alternate cause was found, and she responded to a gluten-free diet. Plates I to L: SN-non-CD patient. Bengali female presenting with diarrhoea, anaemia, night sweats and fevers. Her serum IgA endomysial antibody was negative but duodenal biopsy showed partial villous atrophy with raised intraepithelial lymphocytes. She stained positive for CD8-T-cytotoxic cells but also for CD4-T-helper cells. This could have been mistaken for refractory coeliac disease. However, her HLA-DQ2/8 genotype was negative and on microbiology assessment her duodenal sample revealed mycobacteria (supplementary Figure S1). She was commenced on anti-tuberculosis therapy. Duodenal histology of seronegative villous atrophy (SNVA) and seropositive coeliac disease (SPCD) control. HLA, human leucocyte antigen; SNCD, seronegative coeliac disease; SN-non-CD, seronegative non-coeliac disease.

Survival analysis

There have been 19 deaths within the 200 SNVA cohort, of which 7/60 (11.2%) were in the SNCD group and 12/138 (8.7%) in the SN-non-CD group. In comparison there have been 11/343 (3.2%) deaths in the SPCD controls. On Kaplan-Meier analysis there were no statistical differences in estimated survival between the SNVA groups although this was less favourable compared with SPCD (figure 4: log-rank $p=0.002$).

DISCUSSION

Main findings

We believe that our findings represent a major conceptual change in the understanding and management of SNVA. Having

used a systematic clinical algorithm we have shown that SNCD accounts for 31% of SNVA cases, with the remaining 69% due to SN-non-CD related causes. Furthermore, HLA-DQ2 and/or DQ8 genotype was present in 61% of SNVA cases, with a positive predictive value of only 51% for a diagnosis of SNCD. This is not surprising given that these alleles are common as seen in approximately 40% of the general population.³

Importantly, we have identified that non-white ethnicity is a risk factor to alert clinicians to the possibility of SN-non-CD, in particular with regards to an infective aetiology. These findings are the first to be reported outside of the tropics and in a Western society.²⁵ The clinical relevance of this also expands to the USA where results from a national pathology database have identified that among patients undergoing duodenal biopsies it

Coeliac disease

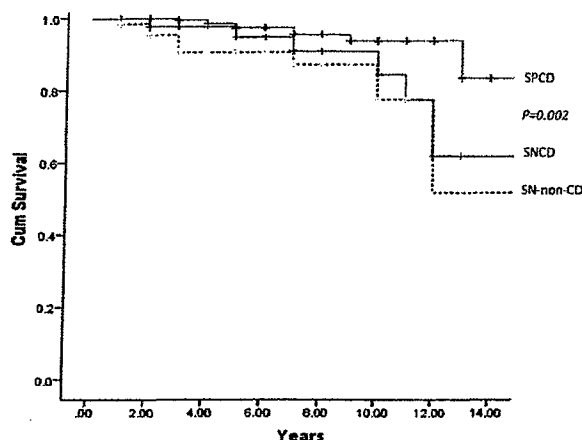


Figure 4 Kaplan-Meier estimated survival curves for seronegative villous atrophy (SNVA) and seropositive coeliac disease (SPCD) controls. SNCD, seronegative coeliac disease; SN-non-CD, seronegative non-coeliac disease.

is those from the Punjab region of India that constitute the ethnic group with the highest prevalence of villous atrophy.⁵² It remains to be determined whether such patients had SNVA given that the US National Health and Nutrition Examination survey has found positive coeliac serology to be rare among non-whites.¹

In addition, in almost one in five cases of SNVA no identifiable cause was found although, reassuringly, the majority spontaneously normalised duodenal histology while being investigated on a gluten-enriched diet; had these patients been commenced on a GFD at the outset instead, they would have erroneously been diagnosed with SNCD and wrongfully subjected to a lifelong, restrictive diet. This, along with previous studies showing an empirical trial of a GFD to be a poor predictor of CD,¹⁷ further supports the notion that clinicians must not start a GFD in SNVA until investigations are complete and a firm diagnosis of SNCD has been established.

Finally, differences in survival outcomes between SNVA and SPCD controls were noted. A recent English study involving more than 10 000 patients with CD found no major excess risk of cancer, digestive disease or respiratory disease related or cardiovascular mortality compared with the general population.⁵³ However, it is recognised that those with SNCD tend to be older and run a more advanced disease course than SPCD.¹⁵ With regards to SN-non-CD this entity has a number of heterogeneous disease associations (ie, HIV, tuberculosis, common variable immunodeficiency) which are associated with poorer outcomes.

Strengths and limitations

The main strength of this study is that it is the largest and most comprehensive to date, having prospectively evaluated 200 consecutive adult patients with SNVA at a UK secondary/tertiary-care centre over a 15-year period. The cohort studied included both inner and outer city referrals. Moreover, systematic and rigorous investigations were performed using testing modalities available among most gastroenterology departments. We therefore feel that our findings can be used as a benchmark and generalised to other physicians seeing similar patients.

However, our study does have several limitations. First, we do not perform serum deamidated gliadin peptide antibodies or intestinal coeliac antibody deposits, both of which are relatively

novel markers and can aid towards the diagnosis of CD.^{54–56} Second, it may also be perceived that by identifying and including IgA deficient patients who were subsequently found to be IgG coeliac serology positive ($n=9$) is a weakness in that this should be common knowledge. However, our findings are those of real life practice and would be supported by other groups who have shown that inadequate evaluation of IgA deficiency occurs frequently when testing for CD.⁵⁷ Nevertheless, had we excluded such patients from our analysis then the prevalence of SNCD would have been 27.7% ($n=53/191$) instead of the 31% ($n=62/200$) stated. Third, we have unanswered questions in those in whom no cause was found (so called idiopathic/unclassified sprue) but spontaneously normalised duodenal biopsies while consuming high-dose gluten. A recent case series has highlighted that self-limiting enteropathies can occur in the context of GI infections,²³ which raises the possibility that our patients may have experienced a similar insult although this was not recalled from their clinical history nor isolated from stool cultures. Furthermore, these individuals had their repeat biopsy performed on average 9 months after the index case which had shown villous atrophy. We do not know when their histology started improving and at what exact time point it had normalised. Had the biopsies been performed earlier then these patients may still have had persisting villous atrophy and, in those with the correct HLA-DQ genotype, subsequently categorised as having CD. However, our study was performed pragmatically and is a reflection of routine outpatient clinical practice. Nevertheless, future research studies should aim to perform biopsies at sequential time points. Finally, of those carrying the HLA-DQ genotype it could be hypothesised that these individuals may still belong to the spectrum of CD and have simply experienced an unexplained GI insult transiently manifesting as SNVA but having not yet reached the cumulative threshold required for CD to become apparent.⁵⁸ Hence, longitudinal follow-up data are now required in this particular group.

Other studies

To our knowledge only one other study has evaluated diagnostic outcomes in SNVA.¹⁶ This was performed by the New York group who evaluated 72 complex case referrals of SNVA over a 10-year period. The investigators found that 22% ($n=16/72$) of their SNVA cases were due to olmesartan-related enteropathy.¹⁶ This novel association has generated substantial interest and is of importance given its presentation may be that of a severe form of enteropathy necessitating hospitalisation for the management of intractable diarrhoea, weight loss, dehydration, hypotension, acute renal failure and metabolic acidosis.^{16 42–45} Yet, these findings are in contrast to ours where the use of A2RB was seen in 8 of 200 SNVA cases, with A2RB a responsible cause for enteropathy in two patients; overall prevalence of A2RB enteropathy being 1% ($n=2/200$). In the other six patients we found an alternate aetiology for SNVA with patients well maintained on their A2RB; these include CD ($n=2$), giardiasis ($n=1$), eosinophilic enteritis ($n=1$), small bowel bacterial overgrowth ($n=1$) and loss to follow-up ($n=1$). Given that A2RBs, including olmesartan, are dispensed in the UK, the discrepancy in the results raises two main points. First, the high prevalence of olmesartan-related enteropathy reported elsewhere may not be reflecting SNVA in general but rather groups overseeing and presenting the outcomes of cases referred from wide catchment areas with presumed 'poorly responsive/refractory CD'.¹⁶ In fact, the initial case series highlighting this association came from the Mayo Clinic where 22 patients with olmesartan-related enteropathy were reported following

referrals from 16 US states over a 3-year period.⁴² Following on, a nationwide multicentre French survey identified 36 patients with olmesartan-related enteropathy.⁴⁴ Most recently, the crude incidence rates of olmesartan and other A2RB enteropathy in France has been calculated at 5.6 and 1.8 per 100 000 patient years, respectively.⁴⁵ These findings suggest that olmesartan-related and in particular other A2RB-related enteropathies are rare adverse events. Second, despite the growing awareness of A2RB-related enteropathy clinicians must still remain vigilant that on occasions A2RBs will merely be innocent bystanders and an alternate aetiology for SNVA will be found.

CONCLUSION

This large UK centre study provides a prospective, systematic and clinically pragmatic evaluation of SNVA. We have shown that most patients with SNVA do not have CD or A2RB enteropathy. Further, a subgroup in whom no cause is found will show spontaneous histological resolution while still consuming gluten and this phenomenon requires further evaluation. The presence of non-white ethnicity was found to be a factor predicting a non-coeliac cause, in particular infective aetiology.

Contributors IA designed the study, recruited patients, collected data, performed statistical analysis, wrote and edited the manuscript. MFP, J-HB, VK, JCW, DP, PV collected data. SSC collected data, performed statistical analysis, and edited the manuscript. PHG edited the manuscript for important intellectual content. DSS conceived and designed the study, recruited patients, collected data, and edited the manuscript. All authors reviewed and approved the final version of the manuscript.

Competing interests None declared.

Ethics approval The initial ethics was from the South Sheffield Research and Ethics Committee, then the Humber Research and Ethics Committee 09/H1304/69. The study was also registered under Sheffield Teaching Hospitals audit number 2954.

Provenance and peer review Not commissioned; externally peer reviewed.

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The clinical and phenotypical assessment of seronegative villous atrophy; a prospective UK centre experience evaluating 200 adult cases over a 15-year period (2000–2015)

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Exhibit G

Questions and Answers on FDA's Adverse Event Reporting System (FAERS)

What is FAERS?

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support the FDA's post-marketing safety surveillance program for drug and therapeutic biologic products. The informatic structure of the FAERS database adheres to the international safety reporting guidance issued by the International Conference on Harmonisation ([ICH E2B \(/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm065004.htm\)](http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm065004.htm)). Adverse events and medication errors are coded to terms in the [Medical Dictionary for Regulatory Activities \(MedDRA\) \(http://www.meddra.org/\)](http://www.meddra.org/) (<http://www.fda.gov/AboutFDA/AboutThisWebsite/WebsitePolicies/Disclaimers/default.htm>) terminology.

How Does FDA Use the Information in FAERS?

FAERS is a useful tool for FDA for activities such as looking for new safety concerns that might be related to a marketed product, evaluating a manufacturer's compliance to reporting regulations and responding to outside requests for information. The reports in FAERS are evaluated by clinical reviewers in the Center for Drug Evaluation and Research (CDER) and the Center for Biologics Evaluation and Research (CBER) to monitor the safety of products after they are approved by FDA. If a potential safety concern is identified in FAERS, further evaluation is performed. Further evaluation might include conducting studies using other large databases, such as those available in the [Sentinel System. \(/Safety/FDASentinelInitiative/ucm2007250.htm\)](http://www.fda.gov/Safety/FDASentinelInitiative/ucm2007250.htm) Based on an evaluation of the potential safety concern, FDA may take regulatory action(s) to improve product safety and protect the public health, such as updating a product's labeling information, restricting the use of the drug, communicating new safety information to the public, or, in rare cases, removing a product from the market.

Who Reports to FAERS?

Reporting of adverse events and medication errors by healthcare professionals and consumers is voluntary in the United States. FDA receives some adverse event and medication error reports directly from healthcare professionals (such as physicians, pharmacists, nurses and others) and consumers (such as patients, family members, lawyers and others). Healthcare professionals and consumers may also report adverse events and/or medication errors to the products' manufacturers. If a manufacturer receives an adverse event report, it is required to send the report to FDA as specified by regulations. The reports received directly and the reports from manufacturers are entered into FAERS.

How Can I Report an Adverse Event or Medication Error to FDA?

The MedWatch site provides information about **voluntary and mandatory reporting (/Safety/MedWatch/HowToReport/default.htm)**.

Can Mandatory Reporters Submit Adverse Events Electronically?

The **FDA Adverse Events Reporting System (FAERS) Electronic Submissions (/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/ucm115894.htm)** site provides drug and therapeutic biological product manufacturers, distributors, packers, and other interested parties with information about FDA Adverse Event Reporting System (FAERS) electronic submissions and instructions on how to electronically submit postmarketing individual case safety reports (ICSRs), with and without attachments.

Do FAERS Data Have Limitations?

FAERS data do have limitations. First, there is no certainty that the reported event (adverse event or medication error) was actually due to the product. FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event. Further, FDA does not receive reports for every adverse event or medication error that occurs with a product. Many factors can influence whether or not an event will be reported, such as the time a product has been marketed and publicity about an event. Therefore, FAERS data cannot be used to calculate the incidence of an adverse event or medication error in the U.S. population.

Are FAERS Data Available to the Public?

FAERS data are available to the public in the following ways:

- **FAERS Statistics (/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/ucm070093.htm)**: provides numbers of reports that FDA has received for drug and therapeutic biologic products over the past ten years.
- **FAERS Data Files (/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/ucm082193.htm)**: provides raw data consisting of individual case safety reports extracted from the FAERS database. A simple search of FAERS data cannot be performed with these files by persons who are not familiar with creation of relational databases.
- Individual case safety reports from the FAERS database can also be obtained by sending a **Freedom of Information (FOI) request to FDA (/RegulatoryInformation/FOI/HowtoMakeaFOIARequest/ucm2007229.htm)**.

Where Else Can I Find Safety Information?

- **Potential Signals of Serious Risks/New Safety Information Identified from the FDA Adverse Event Reporting System (FAERS) (/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/ucm082196.htm)**: quarterly reports on potential serious side effects identified by FAERS.
- **Postmarketing Drug and Biologic Safety Evaluations (/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/ucm204091.htm)**: provides summary information about ongoing and completed postmarketing safety evaluations of adverse experience reports made to FDA for New Drug Applications (NDAs) and Biologic License Applications (BLAs) approved since September 27, 2007.

- Center for Drug Evaluation and Research (CDER): [Drug Safety and Availability \(/Drugs/DrugSafety/default.htm\)](#)
- [Postmarket Drug Safety Information for Patients and Providers \(/Drugs/DrugSafety/Post-marketDrugSafetyInformationforPatientsandProviders/default.htm\)](#)
- [MedWatch: The FDA Safety Information and Adverse Event Reporting Program \(/Safety/MedWatch/default.htm\)](#)

Spotlight

- [The Public's Stake in Adverse Event Reporting \(/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/ucm179586.htm\)](#)

Contact FDA

Toll Free
(855) 543-3784 or
(301) 796-3400
druginfo@fda.hhs.gov (<mailto:druginfo@fda.hhs.gov>)

Human Drug Information

Division of Drug Information

<http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm082585>
(CDER)

Office of Communications

[Feedback Form \(http://www.accessdata.fda.gov/scripts/email/cder/comment.cfm\)](http://www.accessdata.fda.gov/scripts/email/cder/comment.cfm)

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Resources for You

- [MedWatch: The FDA Safety Information and Adverse Event Reporting Program \(/Safety/MedWatch/default.htm\)](#)
- [Drug Safety and Availability \(/Drugs/DrugSafety/default.htm\)](#)
- [Postmarket Drug Safety Information for Patients and Providers \(/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/default.htm\)](#)

More in FDA Adverse Events Reporting System (FAERS)

[\(/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/default.htm\)](#)

FDA Adverse Event Reporting System (FAERS): Latest Quarterly Data Files

[\(/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/ucm082193.htm\)](#)

FDA Adverse Events Reporting System (FAERS) Public Dashboard

Potential Signals of Serious Risks/New Safety Information Identified from the FDA Adverse Event Reporting System (FAERS)

(/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/ucm082196.htm)

FDA Adverse Events Reporting System (FAERS) Electronic Submissions

(/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/ucm115894.htm)

Exhibit H

UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF NEW JERSEY

IN RE: BENICAR (OLMESARTAN)
PRODUCTS LIABILITY LITIGATION

CIVIL ACTION NUMBER:

15-2606

STATUS CONFERENCE

Mitchell H. Cohen United States Courthouse
One John F. Gerry Plaza
Camden, New Jersey 08101
September 30, 2015

B E F O R E:

THE HONORABLE ROBERT B. KUGLER
UNITED STATES DISTRICT JUDGE
THE HONORABLE JOEL SCHNEIDER
UNITED STATES MAGISTRATE JUDGE

A P P E A R A N C E S:

MAZIE SLATER KATZ & FREEMAN

Adam M. Slater, Esquire , Esquire

Tara Sutton, Esquire

Lexi J. Hazam, Esquire

Peter J. Weinberger, Esquire

PENDLEY BAUDIN & COFFIN

Christopher Luke Coffin, Esquire

Attorneys for the Plaintiffs

DRINKER, BIDDLE & REATH

Susan M. Sharko, Esquire

Michael C. Zogby, Esquire

Daniel B. Carroll, Esquire

Certified as true and correct as required by Title 28,
U.S.C., Section 753.

/S/ Theodore M. Formaroli

United States District Court
Camden, New Jersey

1 THE COURT: Good morning, everybody. Please be
2 seated. We're on the record. This is In Re: Benicar MDL,
3 Docket 15-2606. Can we have the names of counsel for -- the
4 lead counsel, anyway.

10:06AM 5 MR. COFFIN: Good morning, your Honor. Chris Coffin
6 for the plaintiffs. We'll have a few different people who are
7 speaking on the plaintiffs' side today, so it might be worth
8 them introducing themselves.

9 MR. SLATER: Adam Slater for the plaintiffs.

10:06AM 10 MS. SUTTON: Tara Sutton for the plaintiffs.

11 MR. WEINBERGER: Peter Weinberger for the plaintiffs.

12 MS. HAZAM: Lexi Hazam for the plaintiffs.

13 MS. SHARKO: Susan Sharko, Drinker Biddle, for the
14 defendant.

10:06AM 15 MR. ZOGBY: Michael Zogby, Drinker Biddle, for the
16 defendant.

17 MR. CARROLL: Daniel B. Carroll, Drinker Biddle, for
18 the defendant.

19 THE COURT: Good morning, everybody. We had a little
10:06AM 20 hiccup this morning but it looks like we're going to have our
21 power back on. And Judge Kugler confirmed we're going to go
22 ahead this afternoon, so it's a good development.

23 This was oral argument on the motion. Three general
24 issues, discovery issues regarding the adverse event reports,
10:07AM 25 foreign documents and the *qui tam* documents. So we will

1 address those issues. And then one of the follow-ups from
2 yesterday was dealing with the custodians. If we have time
3 this morning, we'll touch on that. And my preference would be
4 that if we don't wrap that, wrap that up this morning, after
10:07AM 5 we complete this afternoon's session we can continue with the
6 discovery issues, and then of course we can discuss any issues
7 that anybody wants to discuss regarding discovery, what have
8 you.

9 So let's start with the adverse event reports. It
10:07AM 10 seems to the Court, and correct me if I'm wrong, that there's
11 two general issues, one is what adverse event reports have to
12 be produced, and two, do the source documents have to be
13 produced. I think based on what I've seen, and please correct
14 me if I'm wrong, that at least we're on the same page now,
10:08AM 15 that if additional adverse event reports are going to be
16 searched for they are going to be searched for using the
17 MedDRA terms.

18 Am I right about that, plaintiff?

19 MR. SLATER: Yes.

10:08AM 20 THE COURT: Okay, great. So then why don't we deal
21 with the first issue, which is what MedDRA terms should be
22 used. But before we get to that, I think for background
23 purposes I just had a couple of questions that I think would
24 put this discussion in greater focus.

10:08AM 25 Defendant, we had a question, if there are different

1 versions of the MedWatch form, is it defendant's position that
2 they're only agreeing to voluntarily produce the final version
3 or are they also agreeing to produce any draft versions of the
4 final MedWatch report?

10:09AM

5 MS. SHARKO: So, we do not agree to produce drafts.
6 That would fall under the backup or source file. When -- and
7 I have a little longer answer to your question which I think
8 will put it in context. Every time the company gets new
9 information on a particular patient, whether it's from the
10 litigation or because of the company's investigation, they
11 update the adverse event report and submit it to the FDA. So,
12 assume in a hypothetical case that happens five times, what we
13 are producing is the most recent adverse event report, and
14 that will contain everything that was in the earlier

10:09AM

10:10AM

15 iteration. And in fact, in the back section of the report
16 you'll see usually date, this information added, whether that
17 changes the evaluation, things like that. So by producing the
18 most recent, the plaintiffs are getting everything except the
19 draft. I don't even know if there are drafts, frankly, but
20 they are getting the most recent iteration.

10:10AM

21 THE COURT: I used the word "drafts," I'm not sure if
22 that's really the right word to use. Maybe what I should have
23 said was different versions of the MedWatch form other than
24 the final version that you referred to, that's what I was
25 referring to.

10:10AM

1 MS. SHARKO: Okay.

2 THE COURT: "Draft" may not have been technically the
3 right word. We saw one involuntary report by some
4 unidentified person, which was appropriately redacted under
10:11AM 5 the regs. Is Daiichi then required under some regulation to
6 report that information to the MedWatch program?

7 MS. SHARKO: When the report goes to the FDA, the
8 reporter information is not redacted, the FDA knows who the
9 reporter is, but FDA regulations require us to redact the
10:11AM 10 reporter information before we produce it.

11 THE COURT: Right. But when Daiichi receives an
12 involuntary report is it required to report that involuntary
13 report through the MedWatch system?

14 MS. SHARKO: I'm not sure what your Honor means by
10:12AM 15 involuntary report.

16 THE COURT: Well, some of the forms say mandatory
17 reporting, and I'll show it to you, this is one of the
18 *in camera* documents. Voluntary reporting of adverse events,
19 product problems and product use errors. That was one of the
10:12AM 20 documents I think on the disk.

21 MS. SHARKO: Thank you. Oh, that's just the title of
22 the FDA form up here at the top, Voluntary Reporting, that's
23 the name of the FDA form. That's what they call it.

24 THE COURT: So there's a voluntary reporting and a
10:12AM 25 mandatory reporting?

1 MS. SHARKO: That's a good question. I don't know
2 the answer to that.

3 THE COURT: Because the next, the MedWatch form says
4 mandatory.

10:13AM 5 MS. SHARKO: During the recess I can talk to a
6 regulatory person and see if I could get the answer. I always
7 thought the forms were all the same. And in our production we
8 are not looking at does it say voluntary or mandatory.

9 THE COURT: So let me ask you this question, and
10:13AM 10 these are documents from the disk, this is the one with the
11 stamp on top that says Voluntary Reporting. Presumably this
12 is a report, I'm surmising it's from some practitioner. Okay?
13 This is the report that went through the MedWatch program,
14 right? In Section 5 it says, "Describe event or problem."
10:14AM 15 Okay? The language used in Section 5 from the person who
16 reported this is not identical to the language in Section 5 on
17 the report that plaintiff's going to get. Do you know why
18 there is a difference?

19 MS. SHARKO: I'd have to look at those. Are you
10:14AM 20 saying those are the same report?

21 THE COURT: Correct.

22 MS. SHARKO: Okay. May I look at them for a minute?

23 (Handing.)

24 THE COURT: That Section 5, plaintiff doesn't get
10:15AM 25 this.

1 MS. SHARKO: Yes, they would. It is a MedWatch form,
2 they would get that.

3 THE COURT: Okay. They would get this too? The one
4 that I thought plaintiff didn't get, that was on the disk, and
10:15AM 5 I thought everything on the disk plaintiff didn't get.

6 MS. SHARKO: No. They would get the reports on the
7 disk. So I will have to ask the question, but I believe this
8 is the one that came in from the FDA through the Freedom of
9 Information Act.

10:15AM 10 THE COURT: I think that's right.

11 MS. SHARKO: So what I believe, and I can confirm
12 that, is that the second form is what went directly to the FDA
13 because it's stamped received July, and then when it came to
14 Daiichi, then Daiichi turned around and submitted a form
10:16AM 15 because it says here case description, this is -- it says here
16 in Box 5, "this is an initial theory of case received from the
17 Freedom of Information," etcetera.

18 THE COURT: Okay, that's my question. Now, that
19 document that is on the top, the one with the check in the
10:16AM 20 right corner, that's the page that plaintiffs got that was
21 attached as an exhibit to their papers.

22 MS. SHARKO: Yes.

23 THE COURT: The one I showed you with the stamp that
24 says Voluntary Reporting, that was on your disk.

10:17AM 25 MS. SHARKO: So that would have been in the backup

1 file.

2 THE COURT: So let me ask my question again. The one
3 in the backup file, this page, does plaintiff get that?

4 (Indicating)

10:17AM 5 MS. SHARKO: I don't believe they get this page.

6 THE COURT: See, previously -- there is no intent,
7 obviously, to confuse or anything. You said yes, because it's
8 a MedWatch form, but...

9 MS. SHARKO: I didn't read the document carefully
10:17AM 10 enough.

11 THE COURT: So my question is, the one that says
12 "Voluntary Reporting," does plaintiff get that? Does
13 plaintiff get that?

14 MS. SHARKO: I'd like to check on that.

10:17AM 15 THE COURT: Okay.

16 MS. SHARKO: I don't know the answer to that.

17 THE COURT: Do you want to ask them if they got it?
18 Because it wasn't attached to their papers.

19 MS. SHARKO: I'd rather find out if we produced it.

10:18AM 20 THE COURT: Okay.

21 MS. SHARKO: Thank you.

22 THE COURT: But, Ms. Sharko, am I correct that the
23 description in Section 5 on the voluntary reporting form is
24 not identical to Section 5 on the copy plaintiff got?

10:18AM 25 MS. SHARKO: I would have to compare that

1 word-for-word. Yes, Box 5 looks different but I think that
2 may be a matter of how these are prepared. The question, to
3 me, would be is all the information in Box 5 on the FDA
4 version in Box 5 and 6 on this version, noting that it
10:19AM 5 continues onto the second page.

6 THE COURT: Do you know why it was, if it's -- it's
7 not the exact same words, obviously. My very strong
8 supposition is Daiichi is going to say it's the same
9 information, but it's not worded the same. Do you know why
10:19AM 10 Daiichi changes the wording?

11 MS. SHARKO: So, the second one which was submitted,
12 it says submitted by a healthcare professional, that means
13 that this healthcare professional filled out this form in his
14 or her own way and sent it in to the FDA.

10:19AM 15 THE COURT: Right.

16 MS. SHARKO: Daiichi has a, has a strict way of how
17 you fill these out so they are consistent. So they can't just
18 cut and paste from what someone wrote, they have to follow the
19 company procedures on how to complete this. And I can confirm
10:20AM 20 it, I mean I'll look at it now or during a break and make
21 sure, the information should be the same.

22 THE COURT: Do you think plaintiff is entitled to
23 know the wording that the initial reporter used? Because
24 again, it may be the same information but it's not worded the
10:20AM 25 same way. Is it Daiichi's position that no harm, no foul,

1 they are not entitled to it?

2 MS. SHARKO: So, Daiichi's position is the plaintiffs
3 asked for every backup and source file in existence. And my
4 position for all the reasons set forth in the papers was no.

10:20AM 5 But I have said to the plaintiffs repeatedly since this
6 discussion started, if there is a specific report about which
7 you have a good faith concern and interest, let me know and
8 we'll talk about it. And so if they were to ask me that
9 question about one report, I would go to the client and look
10:21AM 10 at that.

11 THE COURT: Okay. I didn't want to delve too much
12 into the source file issue.

13 In Daiichi's brief, page six, it says something to
14 the effect that the line listings of all adverse events were
10:21AM 15 produced, they were contained in the NVA. Can you explain
16 what that means, the line listings?

17 MS. SHARKO: Yeah. Good question. So FDA
18 regulations specify the format of the report, and I could
19 explain why it's one format or the other but that would take
10:21AM 20 a while. If it meets a certain standard it gets reported as a
21 15 day report in one of those forms that you're looking at; if
22 it meets a different standard, it goes in what is called line
23 listings. You just have a list of the report, that's pursuant
24 to the FDA regulations. And so we have given the plaintiffs
10:22AM 25 all the line listings, line listings are in the NVA, and then

1 they are updated in regular intervals in a regulatory filing.

2 THE COURT: Is line listing deemed less serious than
3 these 15-day reports?

4 MS. SHARKO: "Serious" is a regulatory term, and
10:22AM 5 there is a regulatory definition for "serious," but using
6 "serious" as in the lay sense, yes. A line listing in
7 general, in very broad brush terms, and that would be a line
8 listing if it's not quote-unquote serious under the regulatory
9 definition, I believe; or it's already in the label, it's a
10:23AM 10 label event.

11 THE COURT: I think I saw this in another portion of
12 Daiichi's brief, it says "Defendant agrees to produce GI-based
13 adverse reports not reported to a regulatory body." What does
14 that mean?

10:23AM 15 MS. SHARKO: So that was in Mr. Slater's brief, and
16 that's not true. Mr. Slater, as your Honor knows by now, is a
17 constant fountain of impromptu discovery requests, and at one
18 time that was something that bubbled up in one of the
19 meetings. Our position is we have to have order to this chaos
10:23AM 20 and we need written, precise discovery requests.

21 THE COURT: Is there such a thing as adverse reports,
22 GI-based adverse reports not reported to a regulatory body?

23 MS. SHARKO: No.

24 THE COURT: Does such a thing exist?

10:23AM 25 MS. SHARKO: No.

1 THE COURT: Okay. Bear with me, I've just got some
2 notes.

3 Is there such a thing as a regulatory causality
4 assessment?

10:24AM 5 MS. SHARKO: Yes.

6 THE COURT: Where would that be located?

7 MS. SHARKO: In the adverse event report that we gave
8 to the plaintiffs.

9 THE COURT: It's one of the boxes? What is a
10 regulatory causality assessment?

11 MS. SHARKO: So, going from memory, we're required to
12 have this assessment, usually it's at the very end of the
13 narrative on the last page, make an assessment, and it changes
14 over time, but if -- you have choices; related, not related,
10:25AM 15 some, at one point in time it was possible, things like that.

16 And so the company checks that box when it submits it. It's
17 not -- it's generally a rote decision, the default is to list
18 everything related based on the information that's presented.
19 It's not a causality assessment that an expert would do at
10:25AM 20 trial, it's not a legal determination.

21 So, for example, if someone submitted an adverse
22 event report and said -- in 2015, and said I had sprue-like
23 enteropathy, the company would more likely than not check
24 "related," because it's in the label. Whether that person
10:25AM 25 actually had it, whether it was caused by the product in the

1 legal sense of causation, is a subject that we would do
2 discovery on and litigate.

3 THE COURT: Is Daiichi contesting that Benicar causes
4 sprue-like enteropathy? Yes, my guess is yes in a particular
10:26AM 5 patient, but what about generally?

6 MS. SHARKO: Yes. We contest general causation.

7 THE COURT: Okay. All right, let me turn to
8 plaintiffs.

9 MS. SHARKO: I just -- if I could add one thing. On
10:26AM 10 the issue of the MedDRA terms, I have since the beginning of
11 this, going back like to March or earlier, told the plaintiffs
12 if you have additional MedDRA terms you want us to search,
13 we're open to that. And the plaintiffs sent us earlier this
14 month a list of terms finally, and I have answers to that.

10:26AM 15 THE COURT: That's where I was getting to next.

16 MS. SHARKO: Okay.

17 THE COURT: What is the -- the issue has been joined,
18 you got what you wanted.

19 MS. SHARKO: Yes.

10:27AM 20 THE COURT: You got plaintiffs' list of MedDRA terms.
21 Based upon how things have gone in this case, you're going to
22 say you are going to agree to search for reasonable additional
23 MedDRA terms, right?

24 MS. SHARKO: I am.

10:27AM 25 THE COURT: And now we're going to dispute what's

1 reasonable or not. So what is the dispute?

2 MS. SHARKO: Okay. And I have not shared this with
3 plaintiffs yet. They asked for another 254 terms. We agreed
4 to 16 of these, and I will send them this in a letter.

10:27AM 5 Crohn's disease -- and I'll write it out for the court
6 reporter afterwards --

7 THE COURT: We're going to resolve this right this
8 morning.

9 MS. SHARKO: Okay.

10:27AM 10 THE COURT: So if someone has a list, give it to me
11 and we'll go one by one if we have to.

12 MS. SHARKO: Okay. So, we have -- they have theirs
13 in two groups. In the more discrete group they asked for 20,
14 we agree to 16; we disagree with three and I can explain why,
10:28AM 15 and one they said they wanted, but we already have it.

16 The other group they have is they asked for
17 everything under the system organ class of gastrointestinal
18 disorders, and that system organ class contains 275 terms. We
19 are searching for 41 of those. We can't agree to search for
10:28AM 20 the other 234, which -- I mean among the things listed there,
21 among those terms are tooth loss, chapped lips, dental
22 cavities. So if plaintiffs want to narrow the 234, we'll look
23 at that list.

24 THE COURT: Well, we're doing it right now. Does
10:29AM 25 anyone have a list for me, and we'll go down the list one by

1 one?

2 MS. SUTTON: Your Honor, I have the list.

3 THE COURT: Okay.

4 MS. SUTTON: With respect to the system organ class
10:29AM 5 gastrointestinal disorders. But if I can request leave from
6 you to explain why we wanted all of the preferred terms to
7 fall under the gastrointestinal organ class.

8 THE COURT: Even things related to teeth?

9 MS. SUTTON: When the defendants -- for one thing,
10:29AM 10 it's very easy for them in their Argus database, they organize
11 systems by system organ class. It's a push of a button to
12 generate those reports. When they report to the FDA, when
13 they give the FDA their periodic safety update reports, they
14 go through the events by organ class and then they look at
10:29AM 15 trend. And I think during science day I showed the Court
16 examples of the six-month reporting periods and they, the
17 company, would look at the gastrointestinal side effects and
18 compare them to the previous to see if there was a trend, if
19 perhaps their labeling needed to be changed. They didn't
10:30AM 20 focus on a particular preferred term, which is what they want
21 us to do, they look at the trend in the data then they discuss
22 if there needs to be a labeling change.

23 We want the benefit of seeing that same data, because
24 that's the way they look at it. They don't look at just
10:30AM 25 diarrhea alone -- I mean they do that too, but they look at

1 the trends. And we saw in the periodic safety updates reports
2 that there were upticks, and they were wondering about why
3 that was. So we want the preferred terms for all the
4 gastrointestinal disorders.

10:30AM 5 And Ms. Sharko said they're giving us 41 of the
6 gastrointestinal disorder terms; they're actually only giving
7 us 25. And they've left off just absolutely critical
8 preferred terms that you find in gastrointestinal disorders.

9 We know, because they weren't warnings, that our clients were
10:31AM 10 misdiagnosed. They are willing to give us celiac disease, we
11 know that's a common diagnosis. But we also know from our
12 clients' medical records that they were diagnosed with having
13 food poisoning. Are they going to give that us that preferred
14 term? No. Irritable bowel disease, irritable bowel symptoms,
10:31AM 15 not on their list. Crohn's disease --

16 THE COURT: Does this relate to the issue that
17 because this association was so new it was misdiagnosed?

18 MS. SUTTON: Misdiagnosed, exactly. And we know from
19 our clients' records, and from the scientific literature,
10:31AM 20 Benicar affects the entire GI tract, it doesn't just impact
21 the small intestine. That's one of the reasons the whole
22 system organ class is relevant in this litigation. And it's
23 really not -- they haven't said that it would be burdensome to
24 produce those MedWatch reports.

10:31AM 25 THE COURT: Right.

1 MS. SUTTON: There's also other things that they've
2 left off. They want to give us diarrhea, but there's
3 preferred terms for lots of different kinds of diarrhea; viral
4 diarrhea, infectious diarrhea. Do we get that? No.

10:32AM 5 THE COURT: You got that, Mr. Court Reporter?

6 MS. SUTTON: Some of this gets pretty graphic. A lot
7 of our clients have rectal injuries from having persistent
8 diarrhea for years. Do we get any of the preferred terms
9 dealing with anal or rectal injuries or hemorrhoids? No.

10:32AM 10 THE COURT: Can I ask you a question? I do not want
11 you to reveal work product. Are these terms that you're
12 asking to be searched that the lawyers got together and says
13 we want this or are you working with consultants, experts,
14 what have you, so you can represent to the Court that there
10:32AM 15 was an informed and educated analysis to pick these terms and
16 not just a bunch of lawyers sitting in a conference room who
17 wanted to protect themselves?

18 MS. SUTTON: No, certainly we're working with
19 experts.

10:32AM 20 THE COURT: Okay.

21 MS. SUTTON: I chair the Expert and Science
22 Committee. We're working with leading gastroenterologists.
23 We're working from the literature, the published literature
24 that describes the injury. Like, for example, colon
10:33AM 25 perforation, there is a case report linking olmesartan to

1 colon perforation. Do we get colon perforation under their
2 interpretation? No, we don't. That's another -- there are
3 all sorts of different perforations within gastric
4 perforation.

10:33AM 5 The preferred terms, the way they work in the
6 gastrointestinal disorders system organ class, is there's all
7 sorts of permutations. Like their modifiers, we'll say,
8 instead of saying gastritis we'll say gastric injury. Do we
9 get that, gastric injury? No.

10:33AM 10 So we think that given that it's not going to be
11 burdensome for them to generate all of the gastrointestinal
12 SOC, let's have it. They analyze it, they analyze the trends,
13 and they do it across the organ class. They don't do it in
14 just 25 terms, which is what they want us to do.

10:34AM 15 THE COURT: Okay.

16 MS. SUTTON: You know, I could keep going through the
17 list of things that they have left off. Nausea. I mean
18 they're going to give us vomiting, but they don't want to give
19 us nausea, retching, regurgitation, these are terms that
10:34AM 20 physicians would use to characterize the events when they get
21 reported to the company.

22 Abdominal pain. That goes across probably all of the
23 thousand clients. Do we get that under their interpretation?
24 No. And again, that's in the gastrointestinal side effects.

10:34AM 25 THE COURT: So when these reports are produced to the

1 plaintiffs, for example the ones, the 7,200 pages that you've
2 already received, are you just getting two or three page
3 MedWatch reports?

4 MS. SUTTON: Correct.

10:34AM 5 THE COURT: That's it?

6 MS. SUTTON: And it's about -- it adds up to
7 somewhere around 2,000 reports, and it's under their
8 interpretation of using just the 41 preferred terms. And then
9 there are issues with those MedWatch reports that make them
10:35AM 10 really not useful in the litigation. I know that the
11 defendants said the argument was sophistry, that we said that
12 all the reports have the same date. They are all dated
13 12-4-2014. And they say, well, that's the date they were
14 generated from Argus. But it's important for us to know what
10:35AM 15 is the real date of that MedWatch form, because we need to
16 know when they gave it to the FDA. Because if it's a serious
17 unlisted event, they've got to get it in in 15 days. But we
18 have no ability to figure that out because the date of the
19 report, for all of them, is the same.

10:35AM 20 And I think your Honor noticed yesterday that they
21 redacted where the report -- where the person that they're
22 reporting on resides. If it's a foreign report, they redact
23 that. I don't think where the person is located, located in a
24 foreign country, that's personal identifying information that
10:36AM 25 requires redaction. So, there is a whole host of issues with

1 the MedWatch forms that we've perceived. They're not useful
2 and it's very difficult for us -- Ms. Sharko had said, well,
3 we've given you the PSURs, the NDA, but if we want to take the
4 MedWatch forms and track them back in to look at how they
10:36AM 5 discuss them in the PSUR. We really can't do it. It's just
6 like a big maze, and it doesn't have to be.

7 You know, I've been doing this litigation, kind of
8 litigation for over ten years, and I've never been in a case
9 where the defendants take the position that they don't have to
10:36AM 10 produce the adverse event reports or the source documents. I
11 mean, that's something that gets agreed upon because in these
12 types of cases it's the most critical information. It goes to
13 causation, it goes to notice, failure to warn; it's the
14 fundamental discovery.

10:36AM 15 THE COURT: I got your position.

16 MS. SHARKO: May I respond?

17 THE COURT: Let me turn to Ms. Sharko. I understand
18 the burden argument with regard to the source files, we'll get
19 to that. Where is the burden in the search through the Argus
10:37AM 20 database?

21 MS. SHARKO: The burden, the burden is it's not just
22 the push of a button. You have to find the forms, and before
23 they can be produced they have to be redacted. But let me --

24 THE COURT: What does that mean, find the forms? All
10:37AM 25 the forms are in the database. You use the MedDRA search

1 terms. Pick a number, 5,000 MedWatch forms, quote-unquote,
2 hit. What then is the burden to printing out those 5,000
3 forms?

4 MS. SHARKO: The burden is to print out the forms and
10:37AM 5 do the review and do the redaction.

6 But let's back up, because I think we're missing an
7 important point here. Every form has multiple codes or
8 multiple MedDRA terms, so if someone complained of an anal
9 problem and vomiting and diarrhea, that form would have been
10:38AM 10 produced because we have "diarrhea" as the term.

11 What I have been saying to the plaintiffs since this
12 dialog started is let's have a discussion about this, one on
13 one. We can't have a discussion with Mr. Slater and 11 people
14 on the phone --

10:38AM 15 THE COURT: Those days are over. We're deciding that
16 this morning. You had your time to decide this, so we're
17 doing it right now.

18 MS. SHARKO: Okay.

19 THE COURT: Can I see the terms that are in dispute?

10:38AM 20 MS. SHARKO: Yes. I'd have to -- I'd need a minute
21 to write down the ones we agreed to.

22 THE COURT: We'll go through it.

23 MS. SUTTON: If I can approach, I have the preferred
24 terms for the system organ class gastrointestinal disorders,
10:39AM 25 and I highlighted the 25 terms that the defendants are willing

1 to --

2 MS. SHARKO: Can I have a copy of that report?

3 MS. SUTTON: Yes.

4 THE COURT: So on page one, you want everything that
10:39AM 5 falls under gastrointestinal disorders.

6 MS. SUTTON: Right, for the reasons I've stated. And
7 then there's also another 20 or so terms that are outside this
8 system class, they're described in Exhibit 1 to the reply
9 brief.

10:39AM 10 MS. SHARKO: And so I can give you an answer, like I
11 said, we will agree to --

12 THE COURT: The other, what did you say, 21 terms?

13 MS. SHARKO: Twenty. They have 20.

14 THE COURT: Are they in here, those 20?

10:39AM 15 MS. SUTTON: Excuse me?

16 MR. ZOGBY: No, your Honor.

17 MS. SUTTON: No, they're in Exhibit 1, my letter to
18 counsel.

19 THE COURT: Okay.

10:39AM 20 MS. SUTTON: That we sent on September 9th, and we
21 did ask to meet and confer with counsel but she never
22 responded.

23 THE COURT: Well, we're going to do it right now.

24 So the first issue before the Court is, I'm looking
10:39AM 25 at what you submitted to the Court, and the document is titled

1 "MedDRA Browser. Gastrointestinal disorders (1017947)." You
2 want everything under that?

3 MS. SUTTON: Right. For the reasons we've stated.

4 THE COURT: Right.

10:40AM 5 MS. SUTTON: This is the trends and the adverse
6 events popping up in this organ class are what the defendants
7 track in order to decide if there is a warning, so...

8 THE COURT: And you're representing to the Court that
9 this isn't something that you're asking for because a bunch of
10:40AM 10 lawyers decided that they think it's relevant to the case.

11 And I'm not asking you to reveal work product, but you're
12 representing that this request is derived from an informed
13 analysis and discussions with appropriately qualified experts
14 and consultants?

10:40AM 15 MS. SUTTON: Right. And our understanding, too, of
16 the burden is if in Argus they search for this system organ
17 class of gastrointestinal disorders, that all of the events
18 underneath that that are in the -- set out in these preferred
19 terms are going to come up. So it shouldn't be burdensome to
10:41AM 20 do.

21 MS. SHARKO: But look at the list, Judge, "abdominal
22 hernias and other abdominal wall conditions." That is not
23 possibly an issue here. Diaphragmatic hernias, inguinal
24 hernias.

10:41AM 25 MS. SUTTON: We can go through all the --

1 THE COURT: I get your point. Okay. So, this is one
2 subset, the other is the 20 in your letter...

3 MS. SUTTON: Of September 9th.

4 THE COURT: I have it here, it was attached as an
10:41AM 5 exhibit but at least the version I think was on PACER didn't
6 have the actual list, it just had the letter. So do you have
7 an extra copy of the list?

8 MS. SUTTON: It's just that I have the letter, I
9 don't have a printout from MedDRA of those terms --

10:42AM 10 MS. SHARKO: The letter --

11 MS. SUTTON: -- described in my letter.

12 MS. SHARKO: The letter specified 20 and we agreed to
13 16 of them.

14 THE COURT: Okay. What are the four in dispute?

10:42AM 15 MS. SHARKO: The four -- well, there is only three in
16 dispute. One is listed, we're already searching for that, and
17 that's abnormal loss of weight. The three in dispute are
18 renal failure -- acute kidney injury, renal failure, acute and
19 renal transplant. If someone reports that they had diarrhea,
10:42AM 20 renal failure and dehydration, the plaintiffs will get that
21 report. What we're looking at here are reports of renal
22 failure, acute kidney injury and renal transplant that have
23 nothing to do with GI problems.

24 THE COURT: Plaintiff.

10:42AM 25 MS. SUTTON: Well, that assumes that everything has

1 been coded correctly. There are a number of cases that have
2 been filed where people have experienced renal failure, on
3 renal transplant lists, that is a side effect of dehydration,
4 so we would ask that we get those documents so we can look at
10:43AM 5 those MedWatch reports because maybe the gastrointestinal side
6 effect isn't properly reflected. It doesn't seem like it
7 would be that burdensome, given the --

8 THE COURT: What's the date of your letter?

9 MS. SUTTON: September 9th, it's Exhibit 1.

10:43AM 10 THE COURT: September 9, 2015, Exhibit 1, it's to
11 reply. So is the only issues regarding this MedDRA search
12 terms whether the whole system organ class for GI disorders is
13 going to be searched, plus the 20 terms in your letter?

14 MS. SUTTON: Right.

10:43AM 15 THE COURT: That's what we're down to?

16 MS. SHARKO: Yes.

17 THE COURT: Okay.

18 MS. SHARKO: And as to the three renal terms, I can
19 tell you that there are 1,000 -- I'm sorry, 9 -- I'm sorry,
10:44AM 20 there are 950 reports for those three categories that are not
21 GI related, that don't have any GI terms. And so that would
22 be 950 reports that we would have to review, redact and
23 produce. This MDL is not about people who claim solely renal
24 injury; in fact, the JPML issued an order on that the other
10:44AM 25 day, reports of sprue-like enteropathy, etcetera, etcetera,

1 etcetera.

2 What we're talking about here are people or doctors
3 or lawyers or anybody who writes in to the company and claims
4 renal failure. There are many, many, many, sorry, causes of
10:44AM 5 renal failure that are not associated with sprue or GI
6 problems.

7 MS. SUTTON: Here's an example of why that limitation
8 could become problematic. They have excluded -- they are only
9 giving us 25 of the gastrointestinal preferred terms, when
10:45AM 10 there are numerous terms at issue. Gastric infections, we're
11 not getting. That term could be in conjunction with renal
12 failure. We're not going to get that person, and that's
13 obviously a person that has a gastrointestinal side effect.

14 Or somebody that they classified as irritable bowel disease,
10:45AM 15 which happened a lot, and had renal failure. We're not going
16 to get that adverse event form under their interpretation.
17 That's why we think an independent search of the three, just
18 three categories regarding renal failure that we asked should
19 be done.

10:45AM 20 THE COURT: Okay. Let's turn --

21 MR. SLATER: Your Honor, can I say one brief thing?

22 THE COURT: Yes, Mr. Slater.

23 MR. SLATER: Because I think we're dropping into the
24 weeds. It's very simple, and I think this example that we're
10:45AM 25 on now perfectly exemplifies why we need what we've asked for.

1 The system organ class will capture all of those terms. To
2 start to pick and choose between them will create the
3 potential for important adverse event reports to not getting
4 in our hands. And this also ties together with the source
10:46AM 5 documents, because if, for example, 950 renal claims were only
6 classified as renal, but the source documents show the people
7 also had diarrhea, also had stomach pain, that would have
8 indicated this could be an olmesartan situation, but they
9 didn't put it on the form. That's incredibly important
10:46AM 10 evidence we need to prove our claims. So that's why we need
11 the system organ class, we need the source documents to prove
12 our case.

13 THE COURT: Thank you.

14 MS. SHARKO: What Mr. Slater just said though, he's
10:46AM 15 arguing that Daiichi might have made a mistake, they might
16 have made a mistake, he has no proof of that, and therefore,
17 we should have to spend a million dollars to produce all the
18 source files. I submit that is unfair and inappropriate.

19 THE COURT: Okay. Let's turn to the source file
10:46AM 20 issue. Is it correct that Judge Johnson did not address the
21 source file issue?

22 MS. SHARKO: Yes.

23 MR. SLATER: Your Honor, we think that Judge
24 Johnson's order was incredibly broad because he said all
10:47AM 25 formal or informal reports of adverse events anywhere should

1 be produced. And that includes everything. A report of an
2 adverse event is not just a report by the company in a form to
3 the FDA, it includes an e-mail from a doctor to a sales rep,
4 it includes a phone call to somebody in medical affairs, it
10:47AM 5 includes a conversation with a marketer at a convention of
6 doctors. It includes any form, and they are required under
7 FDA regulations, no matter how this information comes into the
8 company, to escalate that information to the quality assurance
9 and the pharmacovigilance departments.

10:47AM 10 And I don't have their -- we don't have their
11 internal protocols yet, but this would be the first
12 pharmaceutical company in the world not to have standard
13 operating procedures that follow the requirements to then
14 escalate that up for the formation of a file, for evaluation,
10:48AM 15 to call the doctor or call the patient or call the pharmacist,
16 whoever it is that gave this information, even if it was just
17 a conversation on a street corner, and then to report it if
18 necessary after they collect the information. So it includes
19 everything.

10:48AM 20 THE COURT: Okay. Let me ask the question this way.
21 Did Judge Johnson specifically address the source documents?

22 MS. SHARKO: No.

23 MR. SLATER: This issue was not framed in this way
24 because he was so broad that it would include the source files
10:48AM 25 by definition.

1 THE COURT: Okay. I got your position.

2 Ms. Sharko, an adverse event report that we've been
3 talking about, can we agree that we'll consider that a formal
4 complaint as opposed to an informal complaint?

10:49AM 5 MS. SHARKO: No, I mean, not to be difficult, but an
6 adverse event report is an adverse event report. If someone
7 calls the company and complains that Benicar gave them heart
8 palpitations, we file an adverse event report or it goes into
9 a line listing. Any, quote-unquote, complaint of a medical
10:49AM 10 problem goes down that track. There is no alternative.

11 THE COURT: Judge Johnson's order requires Daiichi to
12 produce "all formal and informal complaints or reports of
13 complications or injuries to your clients." We've been
14 focusing on adverse event reports. What is Daiichi doing
10:50AM 15 about producing the formal and informal complaints that Judge
16 Johnson referred to in his order?

17 MS. SHARKO: Our interpretation of that is that, and
18 there are probably complaint documents like there weren't
19 enough pills in the bottle...

10:50AM 20 THE COURT: Yeah, but later on he definitely limited
21 it to the injuries that we're talking about, so that's not,
22 that's not fair for you to say that.

23 MS. SHARKO: Right. But I wasn't done, I was going
24 to say there are probably complaint files that are being
10:50AM 25 produced, but going to what Judge Johnson ordered, all reports

1 such that he described would be an adverse event report or it
2 would be a line listing. So we believe we have complied with
3 that.

4 THE COURT: Okay. The order says all adverse event
10:51AM 5 reports, and, and all formal and informal complaints. So it's
6 clear to this Court that Judge Johnson was not equating
7 adverse event reports with formal and informal complaints,
8 they were different. So my question is what, quote-unquote,
9 formal and informal complaint information is Daiichi
10:51AM 10 producing, and is it your position that the only responsive
11 information to that part of the order is the line listings?

12 MS. SHARKO: The line listings and the adverse event
13 reports. Source files was never briefed or argued before him.

14 THE COURT: All right. So, okay. So I'm clear on
10:52AM 15 that. Just bear with me while I go through my notes on this
16 issue.

17 (Short pause.)

18 MS. SHARKO: I have an answer to one of your early
19 questions. You asked about mandatory versus voluntary. The
10:52AM 20 reason there is a distinction -- thank you, Ms. Brennan -- is
21 that reporting by Daiichi is mandatory as to the FDA,
22 reporting by the public directly to the FDA is voluntary.
23 That's why one form says mandatory and the other says
24 voluntary.

10:52AM 25 THE COURT: Do you have an answer to the question

1 about whether plaintiffs got the voluntary reports?

2 MS. SHARKO: Not yet.

3 THE COURT: That is an important question.

4 MS. SHARKO: Okay.

10:53AM 5 THE COURT: So let's get into the source documents.

6 Plaintiff, I -- I'm sorry, Mr. Slater, let me go back one
7 question back to the defendants. No, I'm confusing this with
8 another issue, I'm sorry.

9 Let me come back to you, Mr. Slater. I don't think
10:53AM 10 there can be any reasonable question that your request for all
11 source documents, backup documents of all adverse event
12 reports that are produced in the case is a monumental effort,
13 with a capital M. Is that necessary in that case? The Court
14 is very skeptical that you need all source documents for every
10:54AM 15 adverse event report, Mr. Slater. I mean I can't conceive of
16 how much money and time that will take.

17 MR. SLATER: They've documented, they've actually
18 defined the number. I believe they said hundreds of thousands
19 of pages, and I'm trying to put my finger on it, but I thought
10:54AM 20 they said it would be about \$1.6 million.

21 THE COURT: Well, I'm not sure if that estimate
22 would, if the Court accepts the additional MedDRA terms that
23 plaintiffs are proposing, I'm not sure that that estimate
24 sticks.

10:54AM 25 MR. SLATER: Well, they haven't argued that. And

1 even though they didn't talk about the letter that we sent
2 them, they had our letter and knew what we were requesting.
3 And for whatever reason, their brief was written as if the
4 letter hadn't been received.

10:55AM 5 Let me try to talk about the balance between the
6 burden and the benefit to us. Because I think they have
7 defined, they said, hundreds of thousands of pages in a case
8 where they've told us that potentially tens of millions of
9 pages of documents are going to be produced is a flyspeck.

10:55AM 10 And we're now at the heart of the case. This entire
11 litigation, every time we ask for something, we're put in a
12 position of having to ask for a broad range of things because
13 we can't get the definition on. When we talked about
14 custodians yesterday, as an example. This is not an area
10:55AM 15 where we should be getting cut back. If there is one area
16 where we shouldn't be getting cut back it's here.

17 And let me give you an example. I read the letter
18 that counsel gave your Honor with the disk, and it talks about
19 the backup documents for those few MedWatch reports, and how
10:55AM 20 in one of them all they have is two pages because it was a
21 licensee, because they have these deals with other pharma
22 companies to handle the marketing in specific countries. So a
23 licensee had the source documents and gave Daiichi two pages,
24 and that's what they used to send in their MedWatch report to
10:56AM 25 the FDA. And we can't even get those other documents yet, we

1 don't know how we're going to get them.

2 Number one, how they can have such a mess of their
3 source documents in light of the FDA regulation that says this
4 has to be accessible if the FDA asks for it is beyond any of
10:56AM 5 us at this side of the courtroom. Because if they can't get
6 those documents, they're in violation of federal regulations.
7 The FDA requires that the backup be available, number one.

8 Number two, the Argus database has the capacity to
9 house all of this in specific fields based on the information
10:56AM 10 we have which is publicly available, and our expert on the IT
11 and the ESI issues -- why they have not been uploading this
12 information as they get it so it would be fully accessible in
13 a central location like we thought it would be is beyond us.
14 If they created a situation where they're housing paper
10:56AM 15 documents around the world so that they'll be hard to get to,
16 that's their problem that they created on their own. And they
17 should have to eat that burden now because they created it for
18 whatever business purposes or for whatever future litigation
19 purposes they may have thought about, or maybe somebody just
10:57AM 20 didn't think about it and is sloppy. But whatever the reason
21 is, we should not be burdened because they chose not to use a
22 complex regulatory management system that's at their
23 fingertips that they're using. That's another point. Any
24 burden is their own -- by their own device.

10:57AM 25 Now, let's break this down a little. They have told

1 the Court that for some of the adverse event reports to the
2 FDA, that they do have the source documents on Argus. We
3 don't know how many; they said for some, for some small
4 number.

10:57AM 5 THE COURT: They've said that to the FDA?

6 MR. SLATER: They said that in their briefs, they
7 said that to us.

8 So the starting point is whatever is on Argus should
9 be produced.

10:57AM 10 THE COURT: Mr. Slater, there is a lot of firepower
11 on your side of the courtroom, you've undoubtedly been through
12 this before, are there particular types or categories of
13 documents in the source or backup files that you're looking
14 for?

10:58AM 15 MR. SLATER: I can tell you what we would expect to
16 be there. Number one, and I'm going to draw on one of the
17 questions you asked counsel earlier today, the causality
18 assessments. They say, well, it's right there on the MedWatch
19 form. What there is is related or not related, okay. What

10:58AM 20 really happens in the real world is as this gets escalated,
21 the quality assurance and the pharmacovigilance departments
22 and medical affairs will interact generally on evaluating
23 these, and there'll be e-mails back and forth. And there will
24 be documents created where they're doing their causality

10:58AM 25 assessment and they're interacting. That's very important.

1 And if there is any draft or if there's multiple
2 forms of MedWatch form, for example they may have filed one in
3 2011, then gotten more information the next year from the
4 doctor. We need to see every one that was filed for a
10:58AM 5 particular patient, we need to see any drafts and any of the
6 backup information where it's being evaluated. We need to see
7 what the initial report was and what any other reports of
8 information were.

9 THE COURT: So if we zero in on why you need to see
10:59AM 10 it, is it because you want to explore that they, that Daiichi
11 should have known about this association/causation before this
12 Mayo Clinic report came out?

13 MR. SLATER: Well, we already know they knew about it
14 before that now, we have e-mails going back to '09 where
10:59AM 15 they're concerned about celiac cases. But what we want to be
16 able to do, and it's for several reasons, one, we need to show
17 notice; two, we need to show notice of the specifics. And
18 that's where the information in the source documents as
19 reported is so critical, because how they chose to frame it
10:59AM 20 and how they chose to describe it to the FDA is not what we're
21 willing to rely on, for the reasons we've talked about which I
22 think are very clear to the Court. So, notice; are their
23 warnings adequate? Is the current warning adequate? We say
24 no, because all of these source documents we believe will show
11:00AM 25 a great deal of information about what they actually knew and

1 the severity, and the different levels of severity, etcetera.

2 So, again, we're talking here about signals, and
3 signals are very important in this case. What they chose to
4 tell the FDA versus -- and the world in their labels versus

11:00AM 5 what they have internally is information about these adverse
6 events that could be critical information in proving claims
7 for plaintiffs in certain cases from certain states because
8 the standards are different in certain states on what you need
9 to have to prove a failure to warn case where there's an FDA

11:00AM 10 approved label. And in certain states the defendants will
11 make the argument, we have to show conduct that's tantamount
12 to directly defrauding or misleading the FDA of information
13 they had. The source documents could very well be the
14 linchpin to certain plaintiffs being able to bring a cause of
11:01AM 15 action to trial in those cases.

16 The causality assessment, we -- frankly, we're
17 stunned. Counsel has taken the position they dispute general
18 causation, they won't admit that it causes sprue-like
19 enteropathy for anybody, that's what I heard counsel tell you
11:01AM 20 earlier. That's what she said, we dispute general causation.

21 THE COURT: So if they dispute general causation,
22 obviously they're going to dispute specific causation.

23 MR. SLATER: In every single case. And all the
24 information and all the offhand notes and all the offhand
11:01AM 25 comments by the Ph.D.'s and the M.D.'s in that company who are

1 tasked with evaluating these are very important. And I'll
2 come back to the example I gave you that came out from their
3 letter. Let's assume that they got a two page document from
4 France, some licensee in France or wherever that person was,
11:01AM 5 saying what's in this MedWatch form, or information that led
6 them to put that in there. We don't know what it was because
7 we don't have the source document. And let's assume that the
8 quality assurance and pharmacovigilance and medical affairs
9 people in the U.S. didn't see that and say whoa, we need to
11:02AM 10 see the rest of the information. Because as of now, counsel
11 has represented to the Court they can't get access to the
12 underlying documents. Does that prove a negligence claim?
13 Does that prove potentially punitive damages are available?
14 Is that a component to those claims? Absolutely. If they
11:02AM 15 stuck their heads in the sand and said we don't want to see
16 the rest of the information, I'd like to depose that person
17 and ask why didn't you want to see the rest of the
18 information?

19 Now, we don't know when they reported any of these to
11:02AM 20 the FDA, but I believe that goes back to 2005 or 2007, those
21 were the two reports. So they have this information and
22 they're not scrambling around the world and getting all that
23 information and doing a very, very thorough evaluation of
24 this? This is the heart of our case.

11:02AM 25 THE COURT: Mr. Slater, how come if these source

1 files are so obviously relevant, why hasn't anyone produced
2 case law to the Court where -- obviously I'm aware of cases
3 where courts have said source files are discoverable, the one
4 or two cases that defendants cite they are not discoverable,
11:03AM 5 but why isn't there just this body of case law that says this
6 is so clearly discoverable despite the burden of producing
7 these source files in these drug cases that you have to
8 produce them?

9 MR. SLATER: Because it's so clearly obvious that it
11:03AM 10 gets produced and it gets agreed to in every case. I mean you
11 have a bunch of lawyers in front of you who are telling you we
12 can't think of a case we've ever worked on --

13 THE COURT: Tens of thousands -- not tens, but
14 thousands of adverse event reports --

11:03AM 15 MR. SLATER: Absolutely.

16 THE COURT: In your other case?

17 MR. SLATER: Absolutely.

18 THE COURT: Are there thousands of adverse event
19 reports?

11:03AM 20 MR. SLATER: Absolutely. Absolutely. I mean it's --
21 I'm lead of counsel for New Jersey in the mesh, I'm
22 interacting with the leadership, I mean that's a 70,000 case
23 MDL. These documents are routinely being utilized.

24 THE COURT: There is a fair amount of case law
11:04AM 25 dealing with medical devices. Is there any reason the Court

1 shouldn't look to those as for relevant support for what the
2 Court should do here, or is there some material difference
3 between medical devices and these drugs that the legal
4 authority in cases discussing medical devices shouldn't apply
11:04AM 5 here?

6 MR. SLATER: I couldn't give you a good reason to say
7 you wouldn't generally look at the cases. You have to look at
8 the specific issues in the case. But, you know, the answer to
9 your question why there's not this massive body of case law is
11:04AM 10 because defendants don't fight this. There's very few cases
11 where this is actually an issue because it's so obviously
12 central to the case. I mean if we're fighting about this,
13 gosh, we're going to, we're going to be in bad shape going
14 forward.

11:04AM 15 THE COURT: Do you need the source files for the
16 litigations like this?

17 MR. SLATER: No.

18 THE COURT: I wouldn't think so. That was my answer
19 as well.

11:04AM 20 MR. SLATER: No, we have that, and we get that with
21 the DFS, we get to see the adverse event report that was filed
22 with the FDA, and the plaintiff presumably has their own
23 documents.

24 THE COURT: There's not going to be anything in there
11:05AM 25 that you don't already have?

1 MR. SLATER: I would hope not. And if the case goes
2 through discovery, I'd assume we'll talk about what other
3 information to do cleanup on. But if they have something, I
4 assume they'll give it to us because, they're supposed to.

11:05AM 5 THE COURT: Okay. Counsel.

6 MS. SHARKO: Four points. First of all, there is no
7 regulation that I'm aware of that says the company has to keep
8 this information, quote-unquote, reasonably accessible. The
9 regulation the plaintiffs cite in their briefs, Section I
10 deals with patient privacy and redactions, and specifically
11 says, to go to one of Ms. Sutton's points, geographical
12 identifiers and adverse drug experience reports are not
13 releasable to the public. The regulation on recordkeeping
14 simply says the applicant, meaning the company, must maintain
15 for a period of ten years all records related to it. So
16 that's what we're required to do, that's what we do.

17 THE COURT: So that's a license to keep the records
18 in an inaccessible bin?

19 MS. SHARKO: Well, the records are not kept in an
11:06AM 20 inaccessible form. Mr. Slater doesn't get to decide how
21 Daiichi, who's never had product liability litigation before,
22 stores their documents. The company believes the documents
23 are stored in a reasonable and logical way. They're not
24 required to say we might have litigation and we might have
11:06AM 25 litigation involving this product and so we need to keep these

1 a certain way. And we're allowed, and there is nothing wrong
2 with having licensees in other countries handle a product.
3 That's routinely done.

4 Number two, this information is not routinely
11:06AM 5 produced. I have never in 35 years of doing pharmaceutical
6 and medical device work had a situation where we had to
7 produce all the source files, or even a large number of source
8 files, for all the reasons that we've argued here to the
9 Court. What always happens in these litigations, in my
11:07AM 10 experience, is the offer I make to the plaintiff at the
11 outset, if there is a particular file you think you need,
12 we'll figure it out.

13 With regard to your question about medical devices,
14 the adverse event reporting regulations and scheme is
11:07AM 15 different for medical devices. Does that mean you can't look
16 at a medical device case? I don't know, I'd have to see that
17 case.

18 THE COURT: Is it materially different, though, for
19 purposes of the legal issues before the Court? Is there
11:07AM 20 something about the medical device cases that would
21 distinguish it -- because there's plenty of medical device
22 cases out there in this area that touch on the issues that
23 we're talking about.

24 MS. SHARKO: The answer is --

11:08AM 25 THE COURT: So far I haven't seen a material

1 difference but, you know, you are the experts.

2 MS. SHARKO: Yes. I'd have to look at, I'd have to
3 look at the case and the issue. I just note that it is two
4 different reporting schemes.

11:08AM 5 And finally, I would say, first of all, obviously the
6 Court can't rely on Mr. Slater's testimony about how the
7 pharmacovigilance department works, but these adverse event
8 reports are chock full of information. When we get
9 information in, we have to tell the FDA what we know, and

11:08AM 10 there are multiple iterations of the report, as I described at
11 the outset. The company cannot just look at some information
12 and say, oh, we're not going to tell the FDA this or that.
13 It's actually for the most part verbatim reporting.

14 THE COURT: Thank you, Ms. Sharko.

11:08AM 15 Any last word for the plaintiff?

16 MR. SLATER: Yes, your Honor. I think you're looking
17 for a practical way to handle this. Let me make a suggestion.
18 First of all, any source documents that are on Argus for any
19 of the -- any of the adverse event reports that are picked up
11:09AM 20 by the MedDRA terms should be produced. I don't know how many
21 there are, they haven't disclosed it. But that's easy. And
22 that's -- there is no reasonable argument they shouldn't give
23 us that, number one.

24 As to the balance, they should be ordered to produce
11:09AM 25 the source documents, and the burden of proof should shift to

1 the defense that if there is a particular one where they want
2 to say we shouldn't have to give you the source document
3 because it's tooth decay or it's toenail fungus, and it's so
4 obviously far afield, as opposed to someone with renal failure
11:09AM 5 or something like osteoporosis or cataracts which do relate to
6 the sequelae from taking a lot of steroids or having
7 malabsorption, then they can come to us on a form by form
8 basis and say, look, you don't need these 50 or 60 or a
9 hundred or whatever it is. We don't know the volume because
11:10AM 10 they haven't told us. And they should have the burden at that
11 point to meet and confer with us and explain why we shouldn't
12 get the source documents for that.

13 And if it's something that's so far afield like those
14 examples they've given like tooth decay, and you know what,
11:10AM 15 tooth decay might be a sequela of malabsorption, if you have
16 malabsorption for eight or nine years, maybe your teeth start
17 to fall apart. I'm not going to say that it's not, but I'm
18 using this colloquially at this time in the argument. The
19 full system organ class, plus the other terms we had, should
11:10AM 20 be searched, and --

21 THE COURT: If we do that, Mr. Slater, isn't it fair
22 to state right now we don't know how many adverse event
23 reports will be identified?

24 MR. SLATER: Well, I would think defense counsel
11:10AM 25 should know, I would assume they've done their homework on

1 this and have a pretty good idea. They never actually told
2 the Court how many didn't get captured by their 41 terms, but
3 that would be captured with this other search. I would think
4 somebody could have done that search in Argus the whole time
11:11AM 5 this issue's been before the Court and has been getting
6 framed. Because we don't even know if there really is that
7 many more. We tend to think there probably are.

8 THE COURT: Well, if there's 950 regarding these
9 three renal categories, I don't know either, but something
11:11AM 10 tells me that there's going to be a lot of hits with the GI
11 category.

12 MR. SLATER: And that would help to prove our case.
13 I mean, that's what we're talking about here is this is --
14 we're now in the eye of the storm. And, you know, we
11:11AM 15 understand the Court is constantly having to balance burdens,
16 and we did that yesterday. We're still -- we're excited to
17 get the defendants' response to our custodian lists, so we can
18 talk about that at some point today. But this is not an area
19 in a case like this where they're disputing general causation,
11:11AM 20 despite the fact that there's all this overwhelming evidence
21 of general causation, where they acknowledged it I believe at
22 science day. I guess we're in a different world now. But
23 they say it's rare, it's only a few different things that
24 happen, and general causation is disputed. We know they're
11:12AM 25 going to fight every issue, to tie our hands on this one I

1 think would be devastating to us because again, the Court
2 doesn't know what we don't know, we don't know. And the most
3 important thing is they have all of this information to work
4 with, they've had it for years.

11:12AM 5 On the native versus TIFF, your Honor made a decision
6 and said okay, you don't have to have the same ability to use
7 this. Our feeling was at that point, okay, we understand the
8 ruling, but when it comes to the actual evidence I think that
9 to give us any less than what they have could be potentially
10 dispositive of this litigation.

11 THE COURT: Okay. Before I rule on the adverse event
12 reports, there's a third sub-issue that I wanted to touch on.

13 Counsel, that's your letter asking for additional
14 information regarding the adverse event reports, database
11:13AM 15 reports, what have you.

16 MR. SLATER: Right.

17 THE COURT: Do you have a resolution of how you are
18 going to handle that? The Court's view is this is a very
19 important part of the case, and many, many times I've said to
11:13AM 20 the plaintiffs or indicated or hinted to the plaintiffs, stop
21 nibbling around the edges and let's get to the heart of it.
22 This is the heart of it, I agree. So, plaintiffs have to get
23 answers to these questions. Are you going to get it from a
24 meet-and-confer, are you going to get it from a 30(b)(6)
11:13AM 25 deposition, how do you resolve this issue?

1 MS. SHARKO: So what I told -- what I told Mr. Slater
2 back in the beginning of August is if you want these
3 documents, serve us with a discovery request, send us a
4 discovery request under the federal rules as to what you want.
11:14AM 5 Because, Judge, you've seen it in this courtroom, it occurs in
6 the space outside of the courtroom, it's constantly, I want
7 this, I want that, send me this, and then the next day a
8 different form.

9 THE COURT: Well, you have in plaintiffs' letter what
11:14AM 10 they want. You have plaintiffs' -- I'm not going to bless a
11 system where every time the plaintiff wants something in this
12 complex case they have to send an interrogatory or an RFP, we
13 have to wait 30 days for a response, there's an objection, you
14 meet and confer, and then 60 days after the request is made
11:14AM 15 the issue is before the Court. That is impractical, and
16 that's not going to happen. We have to deal with these issues
17 in a more prompt fashion.

18 I agree with you, you shouldn't be bombarded with
19 requests. That's a no brainer. You have plaintiffs' letter.
11:14AM 20 You have the questions that plaintiffs want answered. Now,
21 how are they going to get answers to those questions? Do you
22 sit and talk about the questions and answers or does the Court
23 say take a 30(b)(6) deposition, plaintiffs? This is a
24 critical area of the case.

11:15AM 25 MS. SHARKO: We have Ms. Sutton's letter that came in

1 in the middle of briefing. I understand what your Honor is
2 saying, and we will get a response to that letter within two
3 weeks.

4 THE COURT: Okay. Mr. Slater, put this on the agenda
11:15AM 5 for our next two-week phone call. If you don't get
6 satisfactory answers to your questions, raise the issue and
7 the Court is inclined to say, take a 30(b)(6) deposition on
8 this issue and let's just cut to the chase. Why we have to go
9 back and forth with letters on a clearly basic critical area
11:15AM 10 of the case, I don't think it should be necessary. But this
11 is so important that I think you are entitled to this
12 information sooner rather than later. So put that on the
13 agenda for the next call.

14 MR. SLATER: Thank you, Judge. And counsel has --
11:16AM 15 again, Ms. Sutton's letter was a summary. We had requested in
16 writing actually prior to that, if they want to speak and
17 confer with us about the scope of it, we're more than happy to
18 have that conversation.

19 THE COURT: Wouldn't it be easier just to sit at a
11:16AM 20 conference table and talk about the answers to these questions
21 rather than have someone wordsmith an eight page letter?

22 MS. SHARKO: So here's the problem --

23 MR. SLATER: We agree, and --

24 MS. SHARKO: Here's the problem, Judge. It's not --
11:16AM 25 it doesn't come out like that. It's a letter here, an e-mail

1 there. You sit in a room with Mr. Slater and a large group of
2 people, and it's like he's taking your deposition. I
3 understand your point about there shouldn't be formal
4 discovery requests for everything, but at the same time it
11:16AM 5 can't be any time he has an idea, you know, he says it in a
6 meeting, and we have to jump and do the answer. Many of
7 these, most of these things I can't answer these questions, I
8 have to go back to my client. So a meet-and-confer with me or
9 Mr. Zogby or Mr. Carroll or Ms. Brennan answering his
11:17AM 10 questions doesn't work.

11 THE COURT: So maybe that counsels for a 30(b)(6)
12 deposition so plaintiff has one shot at asking their
13 questions, they get their answers, and that's the end of it.

14 MR. SLATER: I'll define it for the Court right
11:17AM 15 now --

16 THE COURT: Maybe we'll do it.

17 MS. SHARKO: I submit that there is a middle and a
18 fairer ground, which is to give us the questions in writing,
19 give us time to talk to the client and find out the answers
11:17AM 20 and to give us a person to talk to, not an army of people.

21 MR. SLATER: Your Honor, if I could, if I could, your
22 Honor --

23 THE COURT: I think we resolve this, if you don't get
24 a satisfactory answer in two weeks, raise it in the phone call
11:17AM 25 and you are just going to get a 30(b)(6) deposition.

1 MR. SLATER: Thank you.

2 THE COURT: And that will be the end of it. It seems
3 to me that's the most direct, simple, straightforward,
4 efficient way to handle this issue. This is such a discrete
11:18AM 5 topic that it's so appropriate for a 30(b)(6) deposition.

6 MR. SLATER: Thank you, your Honor. And I will, just
7 so the Court knows, I will send an e-mail to Ms. Sharko as we
8 walk out of the courtroom for the lunch break, defining
9 exactly what we're asking for so there's no question. It's
11:18AM 10 what's in all of our letters. And I would intend to also
11 include the scope of Argus because I think your Honor
12 expressed yesterday, we've asked for that since early August
13 in the ESI meet-and-confers. That's obviously part of it, and
14 all it's going to say is the procedures, protocols and
11:18AM 15 standard operating procedures for the intake evaluation and
16 analysis of adverse events and the full scope of how Argus is
17 used and what its capabilities are. And that's it.

18 MS. SHARKO: But, see, your Honor, this is the
19 point --

11:18AM 20 MR. SLATER: That's what the letters all say.

21 MS. SHARKO: This is the point. The requests from
22 Mr. Slater mutate like bacteria on a substrate. Ms. Sutton
23 sent this letter, we got it when we were doing the briefing.
24 Your Honor said you thought they were fair questions, you
11:19AM 25 asked me to answer them. I know what they are, and I think

1 that I can get the answers from the client within two weeks.

2 Now Mr. Slater says, well, when he leaves the

3 courtroom he's going to send me another list of homework

4 assignments for two weeks. I can't commit to these future

11:19AM 5 homework assignments, I mean this is what I'm talking about.

6 I'm trying to be cooperative --

7 MR. SLATER: What I just said is in writing already.

8 THE COURT: Okay.

9 MS. SHARKO: This is the letter, we will answer it

11:19AM 10 within two weeks.

11 THE COURT: Just put that on the agenda, the adverse

12 event reports, and I think it does fairly include the Argus

13 database is a discrete area that is critical to the case and

14 it's something that if the plaintiff gets the answers to the

11:20AM 15 questions will help advance the ball on the entire case.

16 MR. SLATER: Thank you, your Honor.

17 THE COURT: I think it's something we're going to

18 move to the front of the list.

19 This is what the Court's order, and I'll write an

11:20AM 20 opinion on it so you'll have all my reasoning, but I'm just

21 summarizing what the Court's ruling is going to be on the

22 adverse event report issue. And I just said it, you know,

23 many, many times in this case I've asked plaintiffs to focus

24 on the meat of the case, the heart of the case. And when we

11:20AM 25 get to this adverse event report issue, I think that's exactly

1 what they are doing. So, as opposed to some other discovery
2 issues, it just seems to the Court that this area is so
3 important to the case and so critical, and I'm not the expert,
4 you are, but thus far this is the most important background
11:21AM 5 information that plaintiffs need in discovery. That if
6 there's a doubt I'm going to balance it in favor of the
7 plaintiffs.

8 So, with regard to the MedDRA search terms, the Court
9 is going to grant plaintiffs' request, they're going to get
11:21AM 10 the system organ -- the GI system organ class MedDRA terms,
11 plus the 20 terms that they asked for. I know defendant
12 raised this issue about the three renal issues, I accept
13 plaintiffs' representation that they didn't pull these terms
14 out of whole cloth, that they've been working with
11:21AM 15 appropriately qualified people, and as the Court has asked
16 them to do, they have sharpened their pencil. And if the
17 plaintiffs legitimately need it, I think they are entitled to
18 it. So the plaintiffs are going to get the MedDRA search
19 terms that they want.

11:22AM 20 With regard to the source files, after reviewing the
21 files last night and this morning, there is no doubt in this
22 Court's mind that these source files are relevant for
23 discovery purposes. Absolutely no doubt. In the short amount
24 of time that we had to review the files, and we spent a lot of
11:22AM 25 time looking at them overnight, it just was just apparent to

1 the Court that for discovery purposes, these source files are
2 relevant.

3 The one example I brought to your attention, counsel,
4 really struck the Court, that it's my understanding, and I
11:23AM 5 could be wrong, that the MedWatch for the 77-year-old, the
6 final version was produced to plaintiffs. I'm surmising that
7 the voluntary report was not produced to plaintiff. I could
8 see how someone could make a very good faith argument that the
9 same information is in both reports, but I looked at it and
11:23AM 10 it's worded differently, and someone can make an argument
11 that, you know, why didn't you word it like the original
12 doctor worded it and why did you change the wording even
13 though the information is essentially the same. Maybe it was
14 completely innocent, I don't know, that's not my job. But for
11:23AM 15 discovery purposes, I think plaintiff is certainly entitled to
16 it.

17 We saw, to my uninformed analysis, different versions
18 of MedWatch forms, I think plaintiffs are entitled to
19 understand and know why there's different versions. It may or
11:24AM 20 may not be because additional information was produced, but
21 plaintiffs being plaintiffs, they might have a more cynical
22 view, that they're trying to put the best flavor or color on
23 the language submitted to the FDA and that's why the wording
24 was different. I don't know. I can't read their minds. So
11:24AM 25 in the Court's view, the source documents are unquestionably

1 relevant to the case. There is case law that supports that
2 view.

3 On the other hand, the Court is not prepared to say
4 at this point that all source files should be produced in
11:25AM 5 discovery. This will be a monumental effort. But it also
6 seems to the Court we do not know at this time how many
7 adverse event reports are going to be at issue in the case
8 because defendants have to do their search with these new
9 terms, they have to produce the MedWatch forms to the
11:25AM 10 plaintiffs. And it just seems to the Court that the decision
11 as to how many and which source files should be produced
12 should await plaintiffs' receipt of the final list of adverse
13 event reports that are identified in discovery. So,
14 unfortunately we're going to be back here regarding how many
11:25AM 15 source files have to be produced.

16 It would, Mr. Slater, it will take a very, very
17 unexpected turn in the case for the Court to say that the
18 source file for every single adverse event report has to be
19 produced. That just -- that would be a very surprising
11:26AM 20 development if we got to that, but unquestionably these
21 documents are important, they are critical to the case,
22 plaintiffs' case. We're not nibbling around the edges now,
23 we're getting to the heart of the case. So some reasonable
24 number of source files are going to be produced, but it just
11:26AM 25 seems to the Court that plaintiffs cannot make an informed

1 decision about which source files to ask for until you get the
2 final list. Okay? That's what the Court's ruling is going to
3 be.

4 The next issue I want to get to is the foreign
11:27AM 5 document issue. I'm okay to proceed. If you all want to take
6 a break -- Mr. Court Reporter, do you want to take a break.

7 THE REPORTER: I'm fine, Judge.

8 MR. COFFIN: Your Honor, on this issue before we move
9 on, just a question about timing. I understand there's a lot
11:27AM 10 going on, but in order for us to get to this identification of
11 source documents that are going to be produced, would we need
12 some deadlines on this?

13 MS. SHARKO: We have produced --

14 THE COURT: 72 something, something pages of AERs.

11:27AM 15 MS. SHARKO: Right. And you now have ordered us to
16 do searches under the 254 new terms. It will take a while to
17 do that.

18 THE COURT: Actually wouldn't it be one? Because
19 don't you have to do a search just under gastrointestinal
11:28AM 20 disorder? If you do a search on that one, however you
21 classify that, doesn't it subsume everything underneath that,
22 so is that a little bit misleading, that you have to do 250
23 more searches?

24 MS. SHARKO: I don't think it's misleading, your
11:28AM 25 Honor. It's not a press of the button, but in addition to

1 getting all these they have to be reviewed and redacted and
2 processed and Bates numbered and put in line. And to answer
3 the question as to how long we need to do that, I'd really
4 like the opportunity to talk to the company and the discovery
11:28AM 5 people, the people who are doing the discovery. I think
6 that's the only fair way to give an answer.

7 THE COURT: So how long will it take to tell
8 plaintiffs how many reports are going to be produced after the
9 person puts the GI number in, plus the 20 additional terms,
11:29AM 10 presumably the computer will spit out a number, we're going to
11 produce x-number, we've identified x-number of reports, how
12 long will that take?

13 MS. SHARKO: But knowing -- I'd like time to find out
14 how long it will take because, your Honor, it's not just
11:29AM 15 getting all those reports, they then have to be de-duped
16 because we've produced over 2,700 reports. Presumably at
17 least some of those will have the hit terms on these new
18 terms, and we don't have to produce those again. So we're
19 going to have to sort through all of that.

11:29AM 20 THE COURT: If you want to save money, why don't we
21 just produce duplicate copies? So you don't have to go
22 through it again.

23 MS. SHARKO: Maybe we'll do that.

24 MR. SLATER: We accept that.

11:30AM 25 MS. SHARKO: Could I have a couple days to talk to

1 the client so I can get you a reasonable answer? Can I have
2 until Monday, or Tuesday I guess?

3 THE COURT: Okay. What the Court is going to say is
4 this, and if there's a reason to change the Court's order
11:30AM 5 we'll change it, if there is good cause we'll change it.
6 Within ten days, defendant is going to tell plaintiff their
7 best estimate of how many additional AER reports were
8 identified in this search. If you say 1,011 and it turns out
9 to be 975, I think that's within the range of reason. We're
11:30AM 10 not asking for an exact number, just a ballpark, and these
11 have to be produced within 30 days. And if there's good
12 cause, you come to the Court and you'll get an extension.
13 Okay? So that's what the presumption is going to be.

14 MS. SHARKO: I was going to ask for 60 days, your
11:31AM 15 Honor. This is going to be an enormous undertaking. We know
16 that there are close to a thousand renal failure reports alone
17 and now we have three other terms, tooth cavities --

18 THE COURT: Can you go back to your client, tell them
19 what the Court ordered, if there is good cause you'll get more
11:31AM 20 time. I can't say it any more clearly. Write me a letter
21 saying this is what it's going to involve, Judge, we can't do
22 it in 30 days, we need these days, you'll get them. Simple as
23 that.

24 MS. SUTTON: Your Honor, just one issue. Ms. Sharko
11:31AM 25 brought up the concept of de-duping, that they're not going

1 reproduce MedWatch forms. But the 27 forms that were produced
2 to us, the date of the report was altered in all of them, so
3 they all bear the same date. We would like them to be
4 reproduced with the actual true date that the report was made,
11:31AM 5 not a computer generated date.

6 THE COURT: Is there really any reasonable question
7 that the plaintiffs are entitled to that information?

8 MS. SHARKO: I don't know if it's possible to do it
9 that way, Judge. I will look into that and get back to them.

11:32AM 10 THE COURT: Okay.

11 MS. SHARKO: Thank you.

12 THE COURT: That's one of the issues you are going to
13 meet and confer about in the next two weeks, and if you can't
14 get it resolved we'll take a 30(b)(6) and end it. Okay?

11:32AM 15 MR. COFFIN: Thank you, your Honor.

16 THE COURT: Why don't we take then a ten-minute break
17 and then we'll go to the foreign issue and the *qui tam* issue.
18 All right?

19 THE DEPUTY CLERK: All rise.

11:32AM 20 (Brief Recess at 11:32 a.m.)

21 THE DEPUTY CLERK: All rise.

22 THE COURT: Good morning, everyone, again. Please be
23 seated. We're back on the record. We're going to proceed to
24 foreign documents.

11:49AM 25 Counsel, I have a question for you before we start on

1 the defendant's foreign document issue.

2 MR. COFFIN: Your Honor, excuse me, before we go to
3 that issue can I just interject one thing?

4 THE COURT: Sure.

11:49AM 5 MR. COFFIN: That is, on the custodian issue, as your
6 Honor asked, we stayed late last evening and provided the
7 defendants with our custodian list. My concern is the flight
8 times that some of us have after the status conference, and we
9 haven't heard --

11:50AM 10 MS. SHARKO: I can solve this. We got the list after
11 6 o'clock, it took some time, he said we could have until the
12 end of the day. We've been working on it. We accept the
13 plaintiffs' list, if those are the custodians they want, then
14 we will produce those custodians with one note, and that is
11:50AM 15 that your Honor said 75 and they gave us 76 names because one
16 person works for Daiichi and for Forest. So we'll do 76 I
17 guess in the spirit of good will, but it was 76.

18 MR. COFFIN: Thank you, your Honor.

19 THE COURT: Thank you.

11:50AM 20 Foreign document issue. Counsel, a question for you.
21 As I read the papers, plaintiffs sharpened their pencil, I
22 have it here, I'll pull it up. I think they're now asking for
23 six or seven categories of information, most of which is
24 focused on the GI issue. Hypothetically, let's pick a
11:51AM 25 country, it doesn't matter to me, let's say Germany.

1 Plaintiffs are objecting, if there's responsive documents to
2 one of the categories that are in Germany, plaintiffs are
3 objecting to producing it. Hypothetically.

4 MR. SLATER: Defendants you mean?

11:51AM 5 THE COURT: Defendants. Let's take an easy one,
6 label or label changes, those documents are in Germany,
7 defendants object to producing them. Suppose hypothetically
8 there is a file in Daiichi U.S., Parsippany, wherever they
9 are. German label changes. Does defendant object to
11:52AM 10 producing that folder? In other words, if instead of these
11 responsive documents being located in a foreign country, if
12 responsive documents are located in the United States or with
13 Daiichi Japan who are parties to the case, do defendants
14 object to producing those documents?

11:52AM 15 MS. SHARKO: No. And I told the plaintiffs back in
16 August, and in fact they've been getting documents like that.
17 When you look at the exhibits to their papers, many of them
18 are in fact documents from other countries.

19 THE COURT: So let's -- the letter would be in
11:53AM 20 plaintiffs' reply brief I think is where they, if I'm right,
21 where there is a copy -- is that where the new letter is,
22 plaintiffs?

23 MS. SHARKO: Yes.

24 THE COURT: Where you -- which exhibit is it.

11:53AM 25 MS. HAZAM: Are you talking about our most recent

1 list, your Honor?

2 THE COURT: Yes.

3 MS. HAZAM: It's actually in the brief itself, it's
4 in our reply brief on page five.

11:53AM 5 THE COURT: Okay.

6 MS. SHARKO: Yes, we got that Friday night.

7 THE COURT: Great. Fantastic.

8 So let's look at those five requests. If documents
9 responsive to those five requests, even though they relate to
11:54AM 10 the one, two, three, four, five, six countries listed, if
11 those documents are in the United States or in Daiichi Japan,
12 is there an objection to producing those?

13 MS. SHARKO: The answer to that question is no, for
14 the first three categories. There is an objection as to
11:54AM 15 number four.

16 THE COURT: How about five?

17 MS. SHARKO: Five, no, as to researchers or
18 academics, but communications with healthcare providers in
19 Japan, if a Japanese doctor calls or writes to Daiichi in
11:54AM 20 Japan and has a question that's unrelated to an adverse event
21 report I think that's, A, not relevant and, B, burdensome.
22 But as to the other things in one, two and three, the rest of
23 five, yes, if that's --

24 THE COURT: So let's take hypothetically
11:55AM 25 category one, labels, package inserts, drafts, etcetera. If

1 there is a folder in Daiichi Japan regarding labels, inserts,
2 drafts from France, there would be no objection to producing
3 that?

4 MS. SHARKO: Correct. We'll produce that.

11:55AM 5 THE COURT: Okay. Let me turn to plaintiffs. Why
6 isn't that a satisfactory first step? Let's agree on, you
7 know, whatever objections there are to the five categories,
8 and start with you'll get what's in the possession, custody --
9 well, I don't want to say that. You'll get what's in the
11:55AM 10 United States and you'll get what's in Japan, even though it
11 relates to these other countries. Why can't we start there,
12 see what you get, you know, maybe there will be nothing in
13 there that really is material. Why do we then have to require
14 defendants to go to Germany, Canada, France, Australia and
11:56AM 15 Spain for documents?

16 MS. HAZAM: Yes, your Honor. Lexi Hazam for
17 plaintiffs. First of all, I don't think what defendants just
18 said is that they will produce all those documents that are in
19 those U.S. or Japanese custodial files. We thought in fact
11:56AM 20 they had agreed to do that, that if there were documents found
21 in defendant's own files, then they would not object to
22 producing them solely on the basis that they could be cast as
23 foreign or relating to events abroad.

24 What I just heard Mr. Sharko say was to the contrary
11:56AM 25 as to some of these categories on our narrowed list. And I

1 think what she's saying is that even if they are in the files
2 of agreed upon and ordered custodians, and identified by
3 agreed upon or ordered search terms, that they could still be
4 withheld fully on the basis that they are foreign.

11:57AM 5 THE COURT: I'm not sure that's what I heard.

6 MS. HAZAM: Okay, we will clarify.

7 MS. SHARKO: No, your Honor, that's not what I said.

8 I said the question they asked me back in August was if a
9 document was otherwise relevant would you withhold it because

11:57AM 10 it came from another country, and I said no. And the exhibits
11 proved that. Your Honor then asked me, looking at these
12 lists, if there -- which is a different question.

13 THE COURT: I heard what you said.

14 MS. SHARKO: Okay.

11:57AM 15 THE COURT: And I think I understand what you said,
16 there was no misunderstanding on my part. As to one, two and
17 three, apparently there's no dispute if these documents are in
18 Daiichi U.S., Daiichi Japan, you're going to get them. There
19 is an issue about number four and part of number five, that's
11:58AM 20 what I heard. So why isn't that a reasonable way to proceed
21 on this foreign document --

22 MS. HAZAM: Putting aside that issue, your Honor,
23 this is obviously a global corporation that operates in over
24 80 countries, it had a global clinical safety and
11:58AM 25 pharmacovigilance committee. Documents we've already seen

1 indicate that that committee plans global objectives and tries
2 to harmonize views on clinical safety as a global unit.

3 THE COURT: Where are they located?

4 MS. HAZAM: The employees are in Germany, the U.K.,
11:58AM 5 Japan and the United States.

6 THE COURT: Wouldn't you surmise, I'm not an expert,
7 but wouldn't you surmise that if the headquarters is in Japan,
8 that someone on that committee is going to be in Japan and
9 that the person in Japan is going to get a copy of these
11:58AM 10 documents? So you're going to get the documents.

11 MS. HAZAM: Perhaps, your Honor. But I would also
12 surmise that there are going to be communications between the
13 U.K. and Germany which we would not get because they would not
14 be in those files that your Honor just described. We have
11:59AM 15 seen documents in the files already produced that we think
16 show the relevance of foreign documents, but those files are
17 certainly not sufficient in our view. We have identified, as
18 your Honor has seen, a very narrow list of categories of
19 documents that go to critical issues of relevance in this
11:59AM 20 case, notice and knowledge.

21 We have limited it to six countries that we chose
22 both because they were the most relevant countries where the
23 defendants had their primary operations brought, and to
24 minimize the burden on defendants both because these are where
11:59AM 25 they have their primary operations and they're frequently in

1 touch with them based on documents we've seen, and because
2 most of them are English speaking countries.

3 THE COURT: Have you seen, and I take for granted you
4 didn't have a complete production, you've seen relevant
12:00PM 5 foreign documents, we're not contesting that. Have you seen
6 any communications thus far, in the production thus far
7 between, hypothetically, Germany and France that you otherwise
8 wouldn't get through Japan?

9 MS. HAZAM: Well we wouldn't, because they are not
12:00PM 10 being produced. In other words, what's in the U.S. custodial
11 files are precisely documents that someone from the U.S. is
12 copied on.

13 THE COURT: Right.

14 MS. HAZAM: To give your Honor an example, there is a
12:00PM 15 2006 e-mail from Stefan Freudenthaler, who is the director of
16 risk management.

17 THE COURT: In Germany?

18 MS. HAZAM: He's located in Germany, he is the
19 director of risk management at the European subsidiary of the
12:00PM 20 company, it's an e-mail that attaches an annual safety report
21 on a study, and that report contains adverse events of a
22 gastrointestinal nature. If the U.K. person he copied on this
23 e-mail were to reply just to him and not to everybody, we
24 would not see that. Your Honor, notice is notice, wherever it
12:01PM 25 takes place.

1 THE COURT: Do you have that e-mail there?

2 MS. HAZAM: I do have a copy, yes.

3 THE COURT: All right. Is there -- is it a chain
4 e-mail, is there a bunch of people who get it?

12:01PM 5 MS. HAZAM: Yes.

6 THE COURT: Do I take it one of those people is going
7 to be in Japan and/or the United States?

8 MS. HAZAM: Yes.

9 THE COURT: So you are going to get that document in
12:01PM 10 discovery.

11 MS. HAZAM: We already got it. What we're seeking,
12 your Honor, is any internal communications between foreign
13 subsidiaries. Again, if someone in France or the U.K.
14 responded to that e-mail without copying everyone on the
12:01PM 15 chain, which we know happens frequently, we would not see it.

16 THE COURT: Do you have any reason to believe right
17 now that there is such a document? Obviously you can't know
18 for sure, but if someone sends an e-mail attaching an
19 important report, copies a bunch of people all over the world,
12:02PM 20 do you have any reason to believe that someone would respond
21 to that in a foreign country and not copy other people?

22 MS. HAZAM: Your Honor, we can't know what we can't
23 know, but I do it all the time. We've certainly seen it in
24 many other mass tort cases like this, which is precisely why
12:02PM 25 courts in those other cases have recognized the relevance of

1 these documents and ordered them discoverable and admissible
2 for that matter. It's precisely why. And we've supplied the
3 Court with an example of a document that was used at trial
4 that would not have been obtained if not for allowing for this
12:02PM 5 kind of foreign discovery.

6 THE COURT: Okay. So if we get to your list,
7 counsel, number four, and I have to tell you in my notes I do
8 have a question mark next to that request, because it wasn't
9 clear to the Court what precisely you are looking for,
12:03PM 10 communications with and among marketers regarding GI side
11 effects of olmesartan. What is it precisely that you are
12 looking for, and is there a way that you could give greater
13 focus to that document?

14 MS. HAZAM: What we were looking for there, your
12:03PM 15 Honor, and again, this request like all of them is now limited
16 to only GI side effects of olmesartan, but not the drug
17 generally. So what we're looking for there would be, for
18 example, a marketer e-mailing Mr. Freudenthaler in Germany and
19 saying --

12:03PM 20 THE COURT: What's a marketer?

21 MS. HAZAM: It's a licensee, a company that develops
22 brochures, a sales rep who interacts with physicians. If they
23 e-mail Mr. Freudenthaler, who's the head of a global
24 committee, and say I was talking to a doctor who mentioned
12:04PM 25 that he believes that this drug causes this problem, or he had

1 this report of a patient who had this problem, and again it
2 would be limited to GI side effects.

3 THE COURT: Let me ask you this question. So we're
4 looking at this holistically, everything total, right?

12:04PM 5 MS. HAZAM: Yes.

6 THE COURT: You got what you want with the
7 custodians, so you have 76 new custodians in addition to
8 whatever it was, 86, that we talked about yesterday. So now
9 you have 150 custodians. You have all these new search terms,
12:04PM 10 right? What are the chances that something of the sort that
11 you just mentioned is not going to be picked up in that
12 search?

13 MS. HAZAM: Based on prior litigation, your Honor, I
14 could not say that chances are low, in fact I think the
12:05PM 15 chances are reasonably high. That's precisely why we want
16 this information. We are willing to agree to a limited number
17 of foreign custodians, we're assuming that this searching will
18 be done by a custodian as other searching was, we're assuming
19 it will be using the same search terms. We're not looking to
12:05PM 20 have those search terms translated or have the documents
21 translated. To the extent there are documents that are
22 duplicative, they obviously can be duped or produce them
23 again. We think that there is a limited burden involved here,
24 and they haven't demonstrated one, whereas we have
12:05PM 25 demonstrated the relevance of this, including the specific

1 examples.

2 THE COURT: I know it's relevant, but why isn't this
3 going to be picked up in the search that's already going to be
4 done?

12:05PM 5 MS. HAZAM: Because we know that there are people
6 abroad, and we're only talking about this limited set of
7 countries here, who are talking amongst themselves and to
8 doctors in their country and to regulators in their country
9 about these issues, and they weren't ending up in the U.S. In

12:06PM 10 other words, no one from the U.S. was copied on this document,
11 or perhaps the e-mail to the U.S. person no longer exists, and
12 so we don't get it. And in many cases those documents
13 actually have been key documents. Not only relevant to
14 finding other documents, but even key trial exhibits.

12:06PM 15 THE COURT: What about counsel's comment on number
16 five, there appears not to be a dispute about researchers or
17 academics, but there is a question about communications with
18 healthcare providers. So I suppose this would be a
19 communication with a doctor in Germany about GI side effects.

12:06PM 20 MS. HAZAM: Yes, I think it is quite within the realm
21 of contemplation that a German doctor would e-mail
22 Mr. Freudenthaler and no one in the U.S., and say I have a
23 patient who's experienced this, or just I am concerned about
24 these effects generally. That would be noted.

12:07PM 25 THE COURT: I'm going to try and read defense

1 counsel's mind here. Tell me if I'm reading your mind
2 correctly, counsel. That if such an e-mail was sent, wouldn't
3 that be reflected in one of the adverse event reports you are
4 going to get?

12:07PM 5 MS. HAZAM: If it's specific --

6 THE COURT: Am I right?

7 MS. SHARKO: Yes, sir.

8 MS. HAZAM: It should be, if it's specific to a
9 patient, we agree. But those e-mails won't necessarily be
12:07PM 10 specific to patients. I've seen plenty of e-mails in other
11 litigations that just talk about, I am concerned about this, I
12 have observed problems with it, I have -- I'm working on a
13 study that may show it. They're not always about a specific
14 patient, and therefore they wouldn't necessarily trigger the
12:07PM 15 obligation to make an adverse event report, if that obligation
16 is always carried out.

17 THE COURT: Okay. Let's hear from the defendants
18 about this.

19 MS. SHARKO: Four points. Number one, this is
12:08PM 20 hypothetical. We can't drive burdensome, peripheral and
21 extraordinarily expensive discovery on a hypothetical, or
22 references to it happened in another litigation. We have to
23 have specifics in evidence. Three, your Honor gets what I was
24 going to say. And four --

12:08PM 25 THE COURT: Educated guess.

1 MS. SHARKO: But a good guess.

2 Four, we can't agree to do European custodians. If
3 we're going to have to go down that road, then we'll have to
4 litigate custody and control and all those issues. I've tried
12:08PM 5 to cooperate and compromise here, but for example Australia,
6 there is no Daiichi subsidiary in Australia, and I told the
7 plaintiff this. In Australia the product is marketed by
8 Merck, which is a licensee. So if you were to say produce
9 Merck's -- produce Australian custodians, we would have to go
12:09PM 10 to Merck and say, Merck, we want the computers of these
11 people.

12 Same thing is true in Canada. There is a Daiichi
13 subsidiary in Canada, but they don't market the product, the
14 product is marketed in Canada by Pfizer, which is a licensee.
12:09PM 15 I don't see how I can go to Pfizer, say turn over the
16 custodians's laptops. France has a licensee called Menarini,
17 and they handle part of it. So it's not as easy as it sounds,
18 it's burdensome, and I submit that it's not necessary.

19 THE COURT: Last word, plaintiff.

12:09PM 20 MS. HAZAM: Yes. I would just say first of all that
21 as to the issue of custody or control, as plaintiffs' motion
22 set forth, the standard is not that it's in the possession of
23 the party, the standard is is it something that's accessible
24 to them in their regular business practice. We clearly have
12:10PM 25 evidence of that, which we've submitted with our motion, they

1 were regularly in touch with people at Merck with regards to
2 Australia and with regards to Canada. Many of these entities
3 are also wholly-owned subsidiaries, and this Court itself has
4 indicated that that constitutes sufficient control.

12:10PM 5 We would also say that there are obviously reasonable
6 limits that we can agree to, and we've tried to talk to the
7 defendants about this. Ms. Sharko raises laptops. We can
8 agree that we don't have to, as a starting point at least, get
9 laptops from a very limited list of foreign custodians. We

12:10PM 10 can agree that we don't have to get paper documents. But as
11 far as e-mail files, there should not be any type of a burden
12 involved. There hasn't been one demonstrated, the defendants
13 don't provide anything other than a reiteration of their per
14 custodian cost for the United States.

12:11PM 15 Finally, I would say that some of these documents on
16 this list may not be in custodian files but in databases, it
17 would also be readily produceable.

18 THE COURT: Okay. Thank you. This is what the
19 Court's ruling is going to be on the foreign document request.

12:11PM 20 I have to give plaintiffs credit here, because I think they
21 really did take the Court's direction to heart. In this
22 September 25th letter, there are five requests for documents.
23 They really did I think to their credit hone in on the
24 relevant issues in the case. So, that's really a step forward
12:11PM 25 from where we originally started.

1 Like the Court said, it's looking at this
2 holistically and the Court, the Court has granted plaintiffs a
3 tremendous amount of leeway with the custodians, a tremendous
4 amount of leeway with the search terms, but they agreed upon
12:12PM 5 that. Unquestionably in the Court's view, the adverse event
6 report issue is, if not the most important, one of the most
7 important issues in the case and that's why the Court gave
8 plaintiffs a tremendous amount of leeway there.

9 But I think we're drifting away from the core of the
12:12PM 10 case when we start talking about documents in the United
11 Kingdom, Germany, Canada, France, Australia and Spain. The
12 Court does not doubt that documents in these countries could
13 be relevant, or are relevant, I mean it doesn't take a genius
14 to surmise that. But then the Court has to evaluate what is
12:13PM 15 the likelihood that there are going to be documents in these
16 countries that are not picked up in all the other searches
17 that the Court is permitting in this case, the searches in the
18 United States and Japan. And frankly, I think the chances of
19 that are slim. Is there, of course, a chance that there is

12:13PM 20 some document in France or Spain that is not going to be
21 picked up in some of these other searches? Of course the
22 answer to that is yes, because no one could be sure with
23 certainty. But I think the likelihood of that is slim.

24 I think a very, very fair compromise of this issue at
12:13PM 25 this point is that if the documents are located in the United

1 States or Japan, even though they relate to the United
2 Kingdom, Germany, Canada, France, Australia and Spain, they
3 have to be produced. The Court agrees that categories one to
4 three are relevant. The Court agrees with defendants that
12:14PM 5 category four is objectionable, it's vague in the Court's
6 mind, and based upon what we've been talking about, the
7 likelihood that there is going to be something that's not
8 picked up someplace else is small. So the objection to number
9 four is sustained. And I also agree with defendants that the
12:14PM 10 category in number five, communications with healthcare
11 providers, is an appropriate objection because I think based
12 upon what we talked about, that's going to be picked up in
13 other places.

14 So, the Court's order is going to provide that
12:15PM 15 documents in Daiichi United States, Daiichi Japan, that are
16 responsive to request one, two, three and five, except for
17 communications with healthcare providers, even though they
18 relate to the United Kingdom, Germany, Canada, France,
19 Australia and Spain, have to be produced. And that's what the
12:15PM 20 order is going to say with regard to the foreign document
21 issue. Everything the Court is saying is without prejudice,
22 if there's good cause in the future to go back, if there's a
23 particular custodian in some foreign country, the Court will
24 hear the application. But in the Court's view, this is an
12:15PM 25 eminently fair and reasonable compromise of this discovery

1 dispute.

2 MS. HAZAM: Your Honor, could I just ask a question
3 to clarify your ruling?

4 THE COURT: Yes.

12:15PM 5 MS. HAZAM: I assume that your ruling is only as to
6 documents that although they are in the possession of Daiichi
7 Japan or Daiichi U.S., relate to foreign doctors, for example?
8 I assume that the Court is not ruling that --

9 THE COURT: No, right.

12:16PM 10 MS. HAZAM: -- that e-mails from U.S. doctors that
11 are in the custody of --

12 THE COURT: No, no, no, no, no, no, no.

13 MS. HAZAM: Okay. It just wasn't clear to me, I
14 wanted to confirm on the record.

12:16PM 15 THE COURT: We're only talking about doctors related
16 to the United Kingdom, Germany, Canada, France, Australia and
17 Spain.

18 MS. HAZAM: Okay. Your Honor, I'm not sure if this
19 is the appropriate time to make this submission, we can do so
12:16PM 20 later, but Mr. Freudenthaler is definitely a custodian who we
21 would like to have added based on his position as director of
22 risk management and head of the Global Clinical Safety and
23 Pharmacovigilance Committee.

24 THE COURT: Request denied. We've done it. You had
12:16PM 25 your chance, you got 76. Done. Finished.

1 MR. SLATER: Can I ask one question, your Honor?
2 Academics and reviewers, which your Honor has ruled are
3 discoverable.

4 THE COURT: Researchers or academics.

12:17PM 5 MR. SLATER: Researchers or academics. Our
6 definition would include investigators that work with the
7 company, consultants and key opinion leaders that they
8 actually pay as consultants and consult with regularly as
9 academics and within that category. I just want to say that
12:17PM 10 if that's acceptable to your Honor, we would appreciate that
11 because they would routinely consult with doctors that they
12 pay as consultants on issues like this, as opposed to an
13 independent doctor who just calls up to say, hey, I have an
14 issue.

12:17PM 15 MS. SHARKO: I mean, no. This is the point I keep
16 making. These requests mutate and expand spontaneously. The
17 plaintiffs gave us this, we've been working on it, we've been
18 talking to the client, and now it's something else.

19 THE COURT: How would you interpret the term
12:17PM 20 researchers or academics, counsel? Communications with
21 researchers or academics.

22 MS. SHARKO: A researcher is somebody who is doing
23 research, whether it's a clinical trial or they are doing
24 research, and they ask a question.

12:18PM 25 THE COURT: Could it be an internal person?

1 MS. SHARKO: An internal person?

2 THE COURT: Someone who works for the company in
3 Germany?

4 MS. SHARKO: Somebody who works for the company,
12:18PM 5 somebody who works for the German subsidiary and sends an
6 e-mail to Japan about a study he or she is doing? Yes, I
7 think that falls within what we've been discussing.

8 THE COURT: Okay. That's the definition the Court
9 accepts for responding to number five.

12:18PM 10 *Qui tam*. Defendants, let me start with you with a
11 question. It sounds like Daiichi produced a lot of documents
12 to the government in connection with their investigation. Is
13 that right?

14 MR. CARROLL: I can't state that is correct or not,
12:19PM 15 your Honor. I can't state with certainty that that's correct.

16 THE COURT: Well, counsel, can you tell me if Daiichi
17 produced any documents to the government in response to their
18 investigation? Isn't that why we're here, because the
19 plaintiffs asked for all the documents that Daiichi produced
12:19PM 20 to the government, so how could you not know what they
21 produced?

22 MS. SHARKO: We did produce documents, I think
23 Mr. Carroll is troubled by a lot.

24 MR. CARROLL: I am troubled by a lot.

12:19PM 25 THE COURT: Okay.

1 MR. CARROLL: I am also troubled by the fact that
2 plaintiffs are not asking for just what was produced to the
3 Department of Justice, their requests are extraordinarily --

4 THE COURT: Okay, Mr. Carroll, let's focus on what
12:20PM 5 the Court is interested in, the documents produced to the
6 government. The documents produced to the government, were
7 they produced in response to subpoenas?

8 MR. CARROLL: To a subpoena, yes.

9 THE COURT: Only one subpoena?

12:20PM 10 MR. CARROLL: A subpoena by the Department of Justice
11 seeking documents; the documents were produced in response to
12 that subpoena.

13 THE COURT: Go ahead, I'm sorry.

14 MR. CARROLL: Go ahead.

12:20PM 15 THE COURT: No, I'm sorry, go ahead.

16 MR. CARROLL: There are also state court actions, and
17 I don't know off of the top of my head if documents were
18 produced in addition in those state court actions, what
19 resulted from the --

12:20PM 20 THE COURT: The state court *qui tam* actions?

21 MR. CARROLL: Yes, sir.

22 THE COURT: You don't know if they were produced? I,
23 maybe I saw depositions. Were there depositions taken in
24 those state court actions?

12:20PM 25 MR. CARROLL: I don't believe so, sir.

1 THE COURT: Okay. Was there only one production of
2 documents by Daiichi in response to a subpoena, or were there
3 supplements?

4 MR. CARROLL: I would suspect, Judge, that there were
12:21PM 5 more than one production.

6 THE COURT: Can you give me a guesstimate of how many
7 documents were produced and whether they were produced in hard
8 copy format or electronic format?

9 MR. CARROLL: To the former, no; to the latter, both.

12:21PM 10 THE COURT: Do you have any sense of how many
11 documents were produced?

12 MR. CARROLL: No.

13 THE COURT: Is there an index to the documents that
14 were produced?

12:21PM 15 MR. CARROLL: I believe there is.

16 THE COURT: Okay. Was that index produced to the
17 government?

18 MR. CARROLL: No, I believe that's internal work
19 product, Judge.

12:21PM 20 THE COURT: When Daiichi produced the documents to
21 the government and when they produced their supplements to the
22 government did they say, here's our documents in response to
23 your subpoena, or was there some sort of letter explaining
24 what documents they produced?

12:21PM 25 MR. CARROLL: Unknown. What I can say, Judge, that

1 any documents that were produced were part of a process that
2 ended with a settlement agreement between Daiichi and the
3 Department of Justice, so there were meet-and-confers, there
4 was negotiation.

12:22PM 5 THE COURT: Is it Daiichi's position that if the
6 plaintiffs served a Freedom of Information Act request that
7 they would not be able to obtain the documents that Daiichi
8 produced to the government?

9 MR. CARROLL: I don't know the answer to that
12:22PM 10 question.

11 THE COURT: I'm asking a lot of questions, counsel,
12 that you don't know the answer to.

13 MR. CARROLL: Well, I can answer other questions.

14 THE COURT: There was an argument in your brief to
12:22PM 15 that effect, there was an argument in the brief that
16 defendants should not have to produce their documents because
17 they wouldn't be produceable pursuant to FOIA. So there was
18 an argument in your brief I think, if I'm wrong about this I'm
19 sorry, that it would be burdensome to produce these documents.

12:22PM 20 MR. CARROLL: They are not --

21 THE COURT: I'm asking you how many documents there
22 are, and you can't tell me, so... I'm asking a lot of relevant
23 questions that I'm not getting an answer to, counsel, I'm
24 sorry. This is basic information.

12:23PM 25 MR. CARROLL: I apologize for not being able to

1 answer your question immediately, Judge. However, it is
2 Daiichi's position that the documents would not be
3 discoverable under FOIA.

4 THE COURT: Why?

12:23PM 5 MR. CARROLL: Because FOIA has an exception, the
6 Freedom of Information Act Exception 4 treats with only the
7 trade secrets and commercial or financial information.
8 Documents are commercial or financial for the purpose of the
9 exception stated in our brief, if it discloses information
10 likely to have either of the following effects: To impair the
11 government's ability to obtain necessary information in the
12 future, or to cause substantial harm to the competitive
13 position of the person from which the information was
14 obtained.

12:24PM 15 THE COURT: We have a discovery confidentiality order
16 in this case that bars the plaintiffs from using any of the
17 discovery that Daiichi produces for anticompetitive purposes,
18 so how if these documents are produced in this case -- I'm
19 sorry. Let me go back. How would production pursuant to a
12:24PM 20 FOIA to the plaintiffs for litigation purposes be an
21 anticompetitive burden?

22 MR. CARROLL: So plaintiffs ask for FOIA --

23 THE COURT: The argument that Daiichi made was that
24 if plaintiffs served a FOIA, they couldn't get these documents
12:24PM 25 because there is a trade secret production under the FOIA

1 regs.

2 MR. CARROLL: Correct.

3 THE COURT: And I'm asking, how in the world are
4 these plaintiffs going to use this information for
12:25PM 5 anticompetitive business purposes?

6 MR. CARROLL: Well, that's not the purpose of the
7 protective order, the purpose of the protective order is to
8 keep documents that are protected from the public purview.

9 THE COURT: And there is a discovery confidentiality
12:25PM 10 order in this case that bars the plaintiffs from using the
11 information and from distributing it to any unauthorized
12 person. So why wouldn't that, I guess I'm trying to get to
13 the bottom of this argument that they couldn't get this
14 pursuant to FOIA because of some trade secret protection.

12:25PM 15 MR. WEINBERG: Your Honor, one point of
16 clarification. They only argue this FOIA exception with
17 respect to the reporting requirements under the corporate
18 integrity agreement, not with respect to the other documents
19 that we've requested.

12:25PM 20 THE COURT: Okay. Counsel, this is what I want to
21 do. I want to take a one-minute break and I want you to
22 confer with your colleagues. I want an answer to the question
23 about how many documents have been produced, okay? That is a
24 basic question. It is unfathomable to this Court that there's
12:26PM 25 not an answer to that question at this table.

1 MS. SHARKO: We have the answer. Thank you,
2 Ms. Brennan.

3 There were 58 productions which totaled about a
4 million pages. It's important to recognize that the documents
12:26PM 5 in that production fall into a couple categories. The first
6 category is that many of those documents related to a product
7 that's not at issue in this litigation. The second category
8 or fact is that if the documents were otherwise relevant and
9 discoverable, they have been produced or will be produced.

12:26PM 10 So, there were a lot of Benicar marketing documents
11 presumably in those million pages, those documents either have
12 been or will be produced here. Whether we gave them to the
13 Justice Department, our position is that that's irrelevant.

14 THE COURT: Is there an objection to producing to
12:27PM 15 plaintiffs the subpoena that the government served on Daiichi?

16 MR. CARROLL: That would be a one-minute break
17 question and answer, sir.

18 THE COURT: And I'm also going to ask is there an
19 objection to producing to plaintiffs the index to the
12:27PM 20 production and copies of the enclosure letters sent to the
21 government. Okay? I'm not talking about the underlying
22 documents.

23 MR. CARROLL: Understood.

24 THE COURT: Because let me just turn over the cards,
12:27PM 25 what I'm thinking, okay? This is -- it just seems to the

1 Court, and correct me if I'm wrong, that the plaintiffs are
2 going to get all of the documents, information, what have you,
3 that the marketing people provided to the doctors at issue in
4 this case. Okay? They are going to get that pursuant to the
12:28PM 5 fact sheet, that's my understanding.

6 MR. CARROLL: That's correct, sir.

7 THE COURT: And plaintiffs want everything on a
8 corporate level, okay? I think you know where I'm going. At
9 least at this time in the case, my leaning is we don't have to
10 go that far in this case at that point. Let plaintiffs get

11 everything regarding the doctors at issue in this case, let
12 you all pick your bellwethers, and then we can revisit the
13 issue about whether we have to go further. But, it just seems
14 to the Court plaintiffs ought to know what's out there, and if

12:28PM 15 they know, if they have a copy of the subpoena, they have a
16 copy of the index and they have copies of enclosure letters,
17 at least they know what exists. And then later on in the case
18 they can sharpen their pencil, and if there's something that
19 they didn't get that they want, they can ask for it. That's

12:29PM 20 where I'm heading. Let's take a five-minute break.

21 MR. CARROLL: Five minutes, Judge?

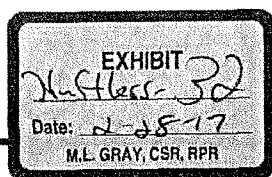
22 THE DEPUTY CLERK: All rise.

23 (During the recess, the proceeding was adjourned.)

24

25

Exhibit I



A method for estimating the probability of adverse drug reactions

The estimation of the probability that a drug caused an adverse clinical event is usually based on clinical judgment. Lack of a method for establishing causality generates large between-raters and within-raters variability in assessment. Using the conventional categories and definitions of definite, probable, possible, and doubtful adverse drug reactions (ADRs), the between-raters agreement of two physicians and four pharmacists who independently assessed 63 randomly selected alleged ADRs was 38% to 63%, kappa (κ , a chance-corrected index of agreement) varied from 0.21 to 0.40, and the intraclass correlation coefficient of reliability ($R[est]$) was 0.49. Six (testing) and 22 wk (retesting) later the same observers independently reanalyzed the 63 cases by assigning a weighted score (ADR probability scale) to each of the components that must be considered in establishing causal associations between drug(s) and adverse events (e.g., temporal sequence). The cases were randomized to minimize the influence of learning. The event was assigned a probability category from the total score. The between-raters reliability (range: percent agreement = 83% to 92%; κ = 0.69 to 0.86; r = 0.91 to 0.95; $R[est]$ = 0.92) and within-raters reliability (range: percent agreement = 80% to 97%; κ = 0.64 to 0.95; r = 0.91 to 0.98) improved ($p < 0.001$). The between-raters reliability was maintained on retesting (range: r = 0.84 to 0.94; $R[est]$ = 0.87). The between-raters reliability of three attending physicians who independently assessed 28 other prospectively collected cases of alleged ADRs was very high (range: r = 0.76 to 0.87; $R[est]$ = 0.80). It was also shown that the ADR probability scale has consensual, content, and concurrent validity. This systematic method offers a sensitive way to monitor ADRs and may be applicable to postmarketing drug surveillance.

C. A. Naranjo, M.D., U. Busto, Pharm.D., E. M. Sellers, M.D., Ph.D., P. Sandor, M.D., I. Ruiz, Pharm.D.,* E. A. Roberts, M.D., E. Janecek, B.Sc. Phm., C. Domecq, Pharm.D.,* and D. J. Greenblatt, M.D.** *Toronto, Ontario*
Clinical Pharmacology Program, Addiction Research Foundation Clinical Institute, and
Departments of Medicine and Pharmacology, University of Toronto

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Reprint requests to: C. A. Naranjo, M.D., Clinical Pharmacology Program, Addiction Research Foundation Clinical Institute, 33 Russell St., Toronto, Ontario M5S 2S1, Canada.

*Clinical Pharmacy Group, Faculty of Chemical Sciences, Universidad de Chile, Santiago, Chile.

**Division of Clinical Pharmacology, New England Medical Centre Hospital, Boston, MA.

The most important problem in assessing adverse drug reactions (ADRs) is whether there is a causal relationship between the drug and the untoward clinical event. The use of the conventional definitions and probabilities of definite, probable, possible, and doubtful ADRs³ generates wide variability in assessment. Koch-

Table I. ADR probability scale

To assess the adverse drug reaction, please answer the following questionnaire and give the pertinent score.

	Yes	No	Do not know	Score
1. Are there previous <i>conclusive</i> reports on this reaction?	+1	0	0	
2. Did the adverse event appear after the suspected drug was administered?	+2	-1	0	
3. Did the adverse reaction improve when the drug was discontinued or a <i>specific</i> antagonist was administered?	+1	0	0	
4. Did the adverse reaction reappear when the drug was readministered?	+2	-1	0	
5. Are there alternative causes (other than the drug) that could on their own have caused the reaction?	-1	+2	0	
6. Did the reaction reappear when a placebo was given?	-1	+1	0	
7. Was the drug detected in the blood (or other fluids) in concentrations known to be toxic?	+1	0	0	
8. Was the reaction more severe when the dose was increased, or less severe when the dose was decreased?	+1	0	0	
9. Did the patient have a similar reaction to the same or similar drugs in <i>any</i> previous exposure?	+1	0	0	
10. Was the adverse event confirmed by any objective evidence?	+1	0	0	
				Total score

Weser et al.⁶ found that clinical pharmacologists frequently disagreed when analyzing the causality of ADRs, and others^{1, 7} have come to similar conclusions. Manifestations of ADRs are nonspecific. The suspected drug is usually confounded with other causes, and often the adverse clinical event cannot be distinguished from manifestations of the disease. Recently there have been attempts to systematize the assessment of causality of ADRs, applying operational definitions such as those proposed by Karch and Lasagna⁸ and by Kramer et al.⁹ The application of these methods in routine clinical practice has been limited, perhaps because they are too detailed and time consuming. We developed a simple method to assess the causality of ADRs in a variety of clinical situations, and its systematic application to different cases of alleged ADRs has provided reliable answers.

Materials and methods

To test the reliability and validity of the ADR probability scale (Table I) several studies were conducted. In the main study, on three occasions (phases 1, 2, and 3) six observers (two physicians and four pharmacists) independently

assessed 63 randomly selected alleged ADRs. These cases composed a stratified random sample (18.8%) of 335 cases of ADRs published during 1978 in the *British Medical Journal* (22 cases), *Lancet* (17 cases), *Annals of Internal Medicine* (12 cases), *Journal of the American Medical Association* (8 cases), and *New England Journal of Medicine* (4 cases).^{*} The cases were randomized to minimize learning, and the sequence was kept blind to the observers.

In the first assessment (phase 1) an "adverse drug reaction" (ADR) was defined as any noxious, unintended, and undesired effect of a drug after doses used in humans for prophylaxis, diagnosis, or therapy. This definition excludes therapeutic failures, intentional and accidental poisoning, and drug abuse.¹⁰ The probability that the adverse event was related to drug therapy was classified as definite, probable, possible, or doubtful.^{5, 12} A "definite" reaction was one that (1) followed a reasonable temporal sequence after a drug or in which a toxic drug level had been established in body fluids or tis-

^{*}A list of the reports will be provided on request.

sues, (2) followed a recognized response to the suspected drug, and (3) was confirmed by improvement on withdrawing the drug and reappeared on reexposure. A "probable" reaction (1) followed a reasonable temporal sequence after a drug, (2) followed a recognized response to the suspected drug, (3) was confirmed by withdrawal but not by exposure to the drug, and (4) could not be reasonably explained by the known characteristics of the patient's clinical state. A "possible" reaction (1) followed a temporal sequence after a drug, (2) possibly followed a recognized pattern to the suspected drug, and (3) could be explained by characteristics of the patient's disease. A reaction was defined as "doubtful" if it was likely related to factors other than a drug.

Six weeks later the 63 cases were reordered randomly and reanalyzed (phase 2). The observers independently assigned a weighted score to the components used to establish a causal association between drugs and adverse events (temporal sequence, pattern of response, withdrawal, reexposure, alternative causes, placebo response, drug levels in body fluids or tissues, dose-response relationship, previous patient experience with the drug, and confirmation by objective evidence). These factors were analyzed and scored using the ADR probability scale (Table 1). Each question could be answered positive (yes), negative (no), or unknown or inapplicable (do not know). The raters were instructed to use the questionnaire for about 20 min.* The ADR was assigned to a probability category from the total score as follows: definite ≥ 9 , probable 5 to 8, possible 1 to 4, doubtful ≤ 0 . The between-raters reliability to use the categorical classification of ADR probability was measured using percent agreement and kappa (κ , a chance-corrected index of agreement).¹⁴ Kappa was calculated as follows:

$$\kappa = \frac{P_o - P_c}{1 - P_c}$$

where P_o = proportion of observed agreement

and P_c = proportion of agreement expected by chance. Kappa ranged from -1 (complete disagreement) to +1 (perfect agreement). Correlation coefficients between ADR scores were also used to test between-raters and within-raters reliability in phases 2 and 3. The intraclass correlation coefficient of reliability ($R(\text{est})$) was also calculated:

$$R(\text{est}) = \frac{S_c^2}{S_c^2 + S_r^2 + S_e^2}$$

where S_c^2 = variance from the cases, S_r^2 = variance generated by the raters, and S_e^2 = residual variance or error. This coefficient is the ratio of the variance associated with true case-to-case variability to the sum of all the components of variance. $R(\text{est})$ varies from zero (i.e., no intercase variation is detected by the ratings, the ratings are the result only of measurement error and between-rater differences) to a maximum of unity (i.e., intercase variation is correctly detected by the ratings, there is no contamination by measurement error or rater-to-rater variation).¹⁴ The $R(\text{est})$ was calculated in phase 1, assuming a score of 1 (doubtful), 2 (possible), 3 (probable), or 4 (definite). The actual ADR scores were used in phases 2 and 3.

To determine whether the improvement in reliability found in phase 2 had occurred by chance the cases were again reordered randomly and reanalyzed independently by the six raters 4 mo later (phase 3). This allowed us to assess within-rater and between-rater retest reliability. The between-rater reliability of practicing physicians was also tested. Three attending physicians independently rated 28 other prospectively collected cases of alleged ADR observed in the Toronto Western Hospital.

Validity. To establish validity comparison with a standard is necessary. Because there is no method that can determine which adverse events are truly ADR, we studied the validity of the ADR probability scale in several ways. Consensual validity was tested as follows. (1) The consensus assessment of three "experts" (C. A. N., E. M. S., D. J. G.) using the conventional categories of ADR probabilities was the external standard with which physicians-pharmacists assessments were compared. Their expertise is supported by publications.^{8, 10, 12}

*An appendix with instructions for using our ADR probability scale will be supplied with reprints and will also be available from the National Auxiliary Publication Service, American Society of Information Services, 1010 16th St. N.W., Washington, D.C. 20036.

Table II. Between-raters agreement

Pairs of raters	Phase 1		Phase 2			Phase 3
	%	κ	%	κ	r	r
R01-R02	52	0.35	83	0.69	0.93	0.85
R04	56	0.37	83	0.70	0.93	0.84
R06	44	0.22	86	0.75	0.92	0.94
R08	49	0.32	87	0.77	0.94	0.89
R10	54	0.35	84	0.72	0.93	0.91
R02-R04	54	0.31	83	0.71	0.91	0.87
R06	49	0.29	89	0.80	0.94	0.87
R08	48	0.32	86	0.75	0.93	0.89
R10	52	0.29	90	0.83	0.95	0.90
R04-R06	54	0.35	84	0.72	0.91	0.87
R08	48	0.36	83	0.70	0.93	0.87
R10	57	0.36	83	0.71	0.91	0.86
R06-R08	46	0.27	92	0.86	0.94	0.91
R10	54	0.35	90	0.83	0.92	0.93
R08-R10	41	0.21	86	0.77	0.94	0.93
Intraclass correlation coefficient of reliability	R(est) = 0.49		R(est) = 0.92			R(est) = 0.87

Table III. Within-raters agreement

Rater	Phase 1 vs. phase 2		Phase 1 vs. phase 3		Phase 2 vs. phase 3		
	%	κ	%	κ	%	κ	r
R01	43	0.23	38	0.16	92	0.85	0.96
R02	67	0.47	63	0.50	86	0.75	0.91
R04	54	0.28	48	0.19	80	0.64	0.94
R06	44	0.22	44	0.22	97	0.95	0.98
R08	36	0.17	43	0.25	87	0.78	0.93
R10	51	0.26	57	0.38	87	0.79	0.97

(2) One of the experts (C. A. N.) assessed the reactions using the ADR probability scale, and his ratings were compared with those by the physicians-pharmacists in phase 2. Content validity was tested in the 63 reported cases and in the 28 prospectively collected cases, comparing the variations in the ADR scores of reactions considered possible, probable, or definite and those classified as definite nondrug adverse events. Concurrent validity was tested by comparing the correlation of the scores of the 63 ADRs obtained by our method with those derived by the algorithm described by Kramer et al.^{2, 9}

Results

Table II shows that there was poor between-raters agreement when the conventional definitions of ADRs were used (phase 1). Percent agreement ranged from 41% to 57% (κ = 0.21 to 0.37, R(est) = 0.49). When the observers applied the ADR probability scale (phase 2) there was a rise in percent agreement (83% to 92%), κ (0.69 to 0.86), and r (0.91 to 0.95) (sign test, $p < 0.001$). The intraclass correlation coefficient of reliability (R[est] = 0.92) indicates high reproducibility. The between-raters reliability was maintained on phase 3 retesting (r = 0.84 to 0.93, R(est) = 0.87). The high within-raters reliability using the ADR probability scale (phase 2 versus phase 3) is shown in Table III. The percent agreement ranged from 80% to 97% (κ = 0.64 to 0.95, r = 0.91 to 0.98). The between-raters reliability of the three attending physicians who rated the 28 prospectively collected ADRs was also high (r = 0.76 to 0.87, R[est] = 0.80).

Validity. Percent agreement between the consensus of experts and the physicians-pharmacists assessments ranged from 79% to 84% (κ = 0.64 to 0.71). Percent agreement with the expert (C. A. N.) who used the ADR probability scale ranged from 86% to 95% (κ = 0.75 to

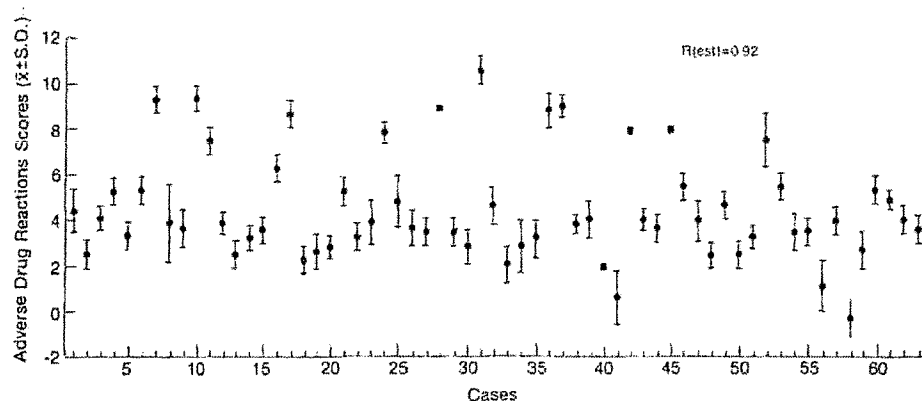


Fig. 1. Distribution of ADR scores in 63 cases of alleged ADRs.

0.91, $r = 0.94$ to 0.96). The ADR scores obtained rating the 63 reported cases with our method correlated with those derived using the algorithm described by Kramer et al.² ($r = 0.82$, $p < 0.001$).

Discussion

Our data indicated a marked improvement in between-raters and within-raters agreement when the adverse events were assessed with our ADR probability scale. The intraclass correlation coefficient of reliability ($R[\text{est}] = 0.92$) suggests that the method can discriminate ADRs of different probabilities. The reproducibility was maintained on retesting, and results of the same order were obtained when physicians rated a different set of prospectively collected cases of ADR. The ADR probability scale is a simple questionnaire that can be answered rapidly.

A major problem in drug-monitoring studies is lack of a reliable method of assessing the causal relation between drugs and adverse events. Such a method is needed because the incidence of adverse events can be estimated only from cases identified as definite or probable ADRs.⁵ Our data and those of others have demonstrated large interobserver variations in assessments when the conventional categorical definitions of probability of ADRs were used.^{1, 7, 8} Our ADR probability scale led to improved reproducibility in assessments. Using our scale, pairs of raters had scores that

were within the same diagnostic category or only one category apart. When there was disagreement it was usually not substantial, as indicated by the small standard deviation of the ADR scores (Fig. 1) and the high correlation coefficients between scores (Tables II and III). A 3-point between-raters disagreement occurred in only one very complicated case.

It is possible that high reproducibility could occur without using the ADR probability scale, but the poor within-raters (phase 1/2 and phase 1/3; Table III) and between-raters agreements (phase 1; Table II) using the conventional definitions rule out this possibility. Perhaps the high agreement occurred because the 63 cases were selected from published reports and included only three ADR categories (possible, probable, and definite), which generated spuriously high reproducibility, but this seems unlikely. Fig. 1 shows that the cases represented a broad spectrum of ADRs (scores ranged from -2 to $+12$). The good correlation between the actual ADR scores reflecting between-raters reliability ($r = 0.91$ to 0.95 ; Table II) and within-raters reliability ($r = 0.91$ to 0.98 ; Table III) and the high κ values suggest that the ADR probability scale was the basis of a genuine improvement in reproducibility. When attending physicians used our method to rate a different set of reactions the between-raters agreement was good ($R[\text{est}] = 0.80$).

Using the ADR probability scale we were also able to identify the origin of the interrater

disagreements. The assessment of question 5 (alternative causes) led to the most disagreement. In view of the complex clinical situations and the differences in training of the observers, this should have been anticipated. Pharmacists in general were more likely to answer "I do not know" to this question. Hutchinson et al.⁴ found that this could be a major source of disagreement even though very detailed instructions were given. In some complicated cases no algorithm can substitute for clinical experience.

Even though the reproducibility of an instrument is important, its validity must also be considered. The observers could agree among themselves, but they could also all be wrong. In cases of adverse events there is no definite standard against which to test the validity of new operational definitions of ADRs. We therefore assessed the validity of our ADR probability scale in several ways. The agreement of the six raters with the consensus of three experts was very high, suggesting that our instrument has consensual validity. Although the experts may not always accurately classify reactions, the probability that the consensus of three experts would be completely wrong all the time is small. The high agreement between the physicians-pharmacists and one of the experts using the ADR probability scale also indicates consensual validity. The concurrent validity of our instrument is suggested by the good correlation between the ADR scores generated by our method and those of another recently published algorithm.² The negative scores in the definite nondrug adverse events and the positive scores in the "true" ADR indicate that our method had content validity. Our findings indicate that our ADR probability scale is reliable and valid.

Important potential applications of the ADR probability scale are the analysis of adverse drug-related events published in medical journals as well as the assessment of reports submitted to national drug monitoring centers. Many countries are interested in developing postmarketing drug surveillance programs.³ The reliability of the ADR assessments in case studies could improve if operational definitions such as ours and similar procedures are used.¹⁵ Advantages of our method are simplicity and wide applicability. Some minor modifications may be

required in special circumstances. In analyzing adverse drug interactions suspect interacting drugs rather than a particular drug must be assessed. When a patient receives several drugs at the same time the ADR scale must be applied to each of the possible causes; the most likely will be the drug with the highest score. In reactions that appear during drug withdrawal, withdrawal corresponds to reinstituting treatment and repetition corresponds to discontinuing the suspect drug.

The conventional classification of definite, probable, possible, and doubtful ADRs, as proposed by Seidl et al.¹³ in 1966, assumes four discrete categories for which there is no empirical demonstration. It is therefore reasonable to postulate that some of the unreliability of the conventional definitions or operational definitions of ADRs could result, because such categories are not unique (i.e., the unreliability could reflect the overlap between nondiscrete categories). Thus the higher correlation coefficients of the actual ADR scores ($r = 0.91$ to 0.94), as compared with the kappa values when using four categories ($\kappa = 0.69$ to 0.83) (Table II), support this view and indicate the need to characterize the probability spectrum of ADRs empirically. We suggest that it is preferable to classify the probability using the actual ADR scores by our and similar operational methods.¹¹

Notwithstanding our encouraging results, it is unrealistic to expect that our relatively simple procedure will solve all the complex problems of identification and classification of ADRs. Further experience will provide the rationale for refinements and improvements and will confirm its utility in clinical practice. Our findings suggest that its systematic application can improve the quality of the assessment of ADRs in a variety of clinical situations.

The collaboration of Doctors M. Spino, H. Wang, and M. Rudyk and of S. Schachter, B.Sc., in some of the phases of the study is gratefully acknowledged.

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Exhibit J



The use of the WHO-UMC system for standardised case causality assessment

Why causality assessment?

An inherent problem in pharmacovigilance is that most case reports concern *suspected* adverse drug reactions. Adverse reactions are rarely specific for the drug, diagnostic tests are usually absent and a rechallenge is rarely ethically justified. In practice few adverse reactions are 'certain' or 'unlikely'; most are somewhere in between these extremes, i.e. 'possible' or 'probable'. In an attempt to solve this problem many systems have been developed for a structured and harmonised assessment of causality (1). None of these systems, however, have been shown to produce a precise and reliable quantitative estimation of relationship likelihood. Nevertheless, causality assessment has become a common routine procedure in pharmacovigilance. The advances and limitations of causality assessment are reviewed in *Table 1*⁽²⁾.

Table 1. Advances and limitations of standardised case causality assessment

What causality assessment can do	What causality assessment cannot do
Decrease disagreement between assessors	Give accurate quantitative measurement of relationship likelihood
Classify relationship likelihood	Distinguish valid from invalid cases
Mark individual case reports	Prove the connection between drug and event
Improvement of scientific evaluation; educational	Quantify the contribution of a drug to the development of an adverse event
	Change uncertainty into certainty

The WHO-UMC causality assessment system

The WHO-UMC system has been developed in consultation with the National Centres participating in the Programme for International Drug Monitoring and is meant as a practical tool for the assessment of case reports. It is basically a combined assessment taking into account the clinical-pharmacological aspects of the case history and the quality of the documentation of the observation. Since pharmacovigilance is particularly concerned with the detection of unknown and unexpected adverse reactions, other criteria such as previous knowledge and statistical chance play a less prominent role in the system. It is recognised that the semantics of the definitions are critical and that individual judgements may therefore differ. There are other algorithms that are either very complex or too specific for general use. This method gives guidance to the general arguments which should be used to select one category over another.

The various causality categories are listed in Table 2. The assessment criteria of the various categories are shown in a point-wise way, as has been developed for practical training during the UMC Training courses.

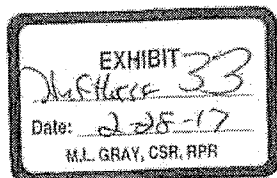




Table 2. WHO-UMC Causality Categories

Causality term	Assessment criteria*
Certain	<ul style="list-style-type: none"> • Event or laboratory test abnormality, with plausible time relationship to drug intake • Cannot be explained by disease or other drugs • Response to withdrawal plausible (pharmacologically, pathologically) • Event definitive pharmacologically or phenomenologically (i.e. an objective and specific medical disorder or a recognised pharmacological phenomenon) • Rechallenge satisfactory, if necessary
Probable/ Likely	<ul style="list-style-type: none"> • Event or laboratory test abnormality, with reasonable time relationship to drug intake • Unlikely to be attributed to disease or other drugs • Response to withdrawal clinically reasonable • Rechallenge not required
Possible	<ul style="list-style-type: none"> • Event or laboratory test abnormality, with reasonable time relationship to drug intake • Could also be explained by disease or other drugs • Information on drug withdrawal may be lacking or unclear
Unlikely	<ul style="list-style-type: none"> • Event or laboratory test abnormality, with a time to drug intake that makes a relationship improbable (but not impossible) • Disease or other drugs provide plausible explanations
Conditional/ Unclassified	<ul style="list-style-type: none"> • Event or laboratory test abnormality • More data for proper assessment needed, or • Additional data under examination
Unassessable/ Unclassifiable	<ul style="list-style-type: none"> • Report suggesting an adverse reaction • Cannot be judged because information is insufficient or contradictory • Data cannot be supplemented or verified

*All points should be reasonably complied with

The use of the WHO-UMC system

To illustrate how the system works, we suggest to first making a comparison of the criteria and wording of 'Probable' and 'Certain'. First of all there is one more criterion in the category 'Certain', the fourth: 'Event definitive pharmacologically or phenomenologically', i.e. an objective and specific medical disorder or a recognised pharmacological phenomenon (for instance 'grey baby syndrome' and chloramphenicol, or anaphylaxis immediately after the administration of a drug that had been given previously). This means that any other event is automatically excluded and can never qualify for 'Certain' (even in the case of a positive rechallenge observation). For 'Certain', rechallenge information with a satisfactory outcome is requested (i.e. what has happened when the drug was first stopped



and later on resumed)), unless the evidence in the report is already convincing without a re-exposure.

For 'Probable', on the other hand, a rechallenge is not required. To qualify as 'Certain' the interval between the start of the drug and the onset of the event must be 'plausible'; this means that there is in sufficient detail a positive argument in support of the view that the drug is causally involved, pharmacologically or pathologically. For 'Probable' the time relationship should be 'reasonable'; this is a more neutral term covering everything that is not unreasonable. Also, with regard to the second criterion, 'alternative causes', the wording is different in 'Probable'. For 'Certain' the occurrence of the event cannot be explained by any disease the patient is known to have or any other drug taken. For 'Probable', on the other hand, the event is 'unlikely' to be attributable to another cause. Also the dechallenge situations (i.e. what happened after stopping) are different. In a 'Certain' case report, the course of events constitutes a positive argument in favour of holding the suspected drug responsible, in pharmacological or pathological respects, whereas in a 'Probable' case it is sufficient if it is 'clinically reasonable' (i.e. not unreasonable).

The essential distinctions between 'Probable' and 'Possible' are that in the latter case there may be another equally likely explanation for the event and/or there is no information or uncertainty with regard to what has happened after stopping.

The criteria that may render the connection 'Unlikely' are firstly the time relationship is improbable (with the knowledge at the time), and/or another explanation is more likely. The term 'Unclassified/Conditional' is of a preliminary nature and is appropriate when, for a proper assessment, there is more data needed and such data are being sought, or are already under examination. Finally when the information in a report is incomplete or contradictory and cannot be complemented or verified, the verdict is 'Unclassifiable'.

Since by far the most frequent categories in case reports are 'Possible' and 'Probable', the usual approach to using the system is to choose one of these categories (depending on the impression of the assessor) and to test if the various criteria fit with the content of the case report. If the report seems stronger one can go one step 'higher' (e.g. from 'Possible' to 'Probable'), if the evidence seems weaker one should try a 'lower' category. To see if that category is the right one or if it does again not seem to fit, the next adjacent term is tried.

For drug-drug interactions the WHO-UMC system can be used by assessing the actor drug, which influences the kinetics or dynamics of the other drug (which has usually been taken over a longer period), in the medical context of the patient.



Summary description of Causality Assessment

Term	Description	Comment
Certain	A clinical event, including laboratory test abnormality, occurring in a plausible time relationship to drug administration, and which cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the drug (dechallenge) should be clinically plausible. The event must be definitive pharmacologically or phenomenologically, using a satisfactory rechallenge procedure if necessary.	It is recognized that this stringent definition will lead to very few reports meeting the criteria, but this is useful because of the special value of such reports. It is considered that time relationships between drug administration and the onset and course of the adverse event are important in causality analysis. So also is the consideration of confounding features, but due weight must be placed on the known pharmacological and other characteristics of the drug product being considered. Sometimes the clinical phenomena described will also be sufficiently specific to allow a confident causality assessment in the absence of confounding features and with appropriate time relationships, e.g. penicillin anaphylaxis.
Probable/ Likely	A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, unlikely to be attributed to concurrent disease or other drugs or chemicals, and which follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfil this definition.	This definition has less stringent wording than for "certain" and does not necessitate prior knowledge of drug characteristics or clinical adverse reaction phenomena. As stated no rechallenge information is needed, but confounding drug administration underlying disease must be absent.
Possible	A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, but which could also be explained by concurrent disease or other drugs or chemicals. Information on drug withdrawal may be lacking or unclear.	This is the definition to be used when drug causality is one of other possible causes for the described clinical event.
Unlikely	A clinical event, including laboratory test abnormality, with a temporal relationship to drug administration which makes a causal relationship improbable, and in which other drugs, chemicals or	This definition is intended to be used when the exclusion of drug causality of a clinical event seems most plausible.



	underlying disease provide plausible explanations.	
Conditional/ Unclassified	A clinical event, including laboratory test abnormality, reported as an adverse reaction, about which more data is essential for a proper assessment or the additional data are under examination.	
Unassessible/ Unclassifiable	A report suggesting an adverse reaction which cannot be judged because information is insufficient or contradictory, and which cannot be supplemented or verified.	

Exhibit K

ROBINS  KAPLAN LLP

300 LASALLE AVENUE
SUITE 2300
MINNEAPOLIS, MINN. 55402

612.349.3400 TEL
612.349.3577 FAX
ROBINSKAPLAN.COM

TARA D. SUTTON
612.349.3577 TEL
TSUTTON@ROBINSKAPLAN.COM

November 30, 2016

Via Electronic Service

Susan Sharko, Esq.
Drinker Biddle & Reath LLP
600 Campus Drive
Florham Park, New Jersey 07932-1047

Re: In re Benicar (Olmesartan) Products Liability Litigation,
MDL No. 2606
NJ MCL Case No. 299

Dear Ms. Sharko:

Please find attached the Expert Report of Daniel Leffler, M.D., served on behalf of Plaintiffs in the above-referenced litigations.

Sincerely,



Tara D. Sutton

cc: Jessica Brennan, Esq. (*via electronic mail*)
Michael Zogby, Esq. (*via electronic mail*)
Adam Slater, Esq. (*via electronic mail*)
Chris Coffin, Esq. (*via electronic mail*)
Rayna Kessler, Esq. (*via electronic mail*)

Attachment

EXPERT REPORT OF DANIEL LEFFLER, M.D.

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I. EDUCATION AND EXPERIENCE

1. I am the Director of Research at the Celiac Center and the Director of Quality Improvement for the Division of Gastroenterology at Beth Israel Deaconess Medical Center, in Boston, Massachusetts. I am an Associate Professor of Medicine at Harvard Medical School and serve as the Associate Director of Research for Quality Improvement, Department of Medicine. I am the Associate Firm Chief in the Department of Medicine at Beth Israel Deaconess Medical Center. I am certified in Gastroenterology by the American Board of Internal Medicine since 2008 and serve on the Intestinal Disorders Section for the American Gastroenterological Association.

2. In July, 2016 I accepted a position as a Medical Director in the Gastrointestinal Therapeutics Area at Takeda Pharmaceuticals. In this role, I assist in the evaluation of the clinical efficacy and safety of novel therapies for gastrointestinal diseases.

3. Over the past decade I have worked extensively in intestinal diseases, focusing on celiac disease and related intestinal malabsorptive disorders. I have treated hundreds of patients with chronic digestive disorders and routinely perform endoscopic procedures for diagnosis and management. I have served as a clinical investigator in studies involving a number of issues, including: gastrointestinal endoscopy safety; gluten free diet adherence; HLA testing in celiac disease; mesalamine as a treatment for celiac disease; celiac disease biomarkers; and celiac disease diagnosis education. I am a founding member and past Secretary for the North American Society for the Study of Celiac Disease, on the medical advisory board for the National Foundation for Celiac Awareness and the Celiac Disease Foundation and served on the Steering Committee Member for the FDA Gastrointestinal Regulatory Endpoints and Advancement of Therapeutics Conference on Celiac Disease.

4. I have authored and edited more than 100 scientific publications on gastroenterology topics, predominantly on celiac disease and related small intestinal disorders including clinical presentation, diagnosis, management and pathophysiology. I have also authored multiple textbook chapters including one on celiac disease for the 2015 Yamada's Textbook of Gastroenterology, 6th ed, and one on small intestinal diseases including celiac disease for the Digestive Diseases Self-Education Program (DDSEP) 8 for the American Gastroenterology Association. I am currently on the editorial board for Clinical Gastroenterology and Hepatology and the World Journal of Gastroenterology and serve as an ad hoc reviewer for more than 20 other peer reviewed journals including the New England Journal of Medicine, the Journal of the American Medical Association, and Gastroenterology. My *curriculum vitae* is attached.

5. I have received numerous honors and awards in my career. I have, for example, received: the Presidential Poster Award from the American College of Gastroenterology (2006); AstraZeneca Senior Fellow Abstract Award, American College of Gastroenterology(2007); PCIR Junior Investigator Laboratory Support Award, Harvard Catalyst (2010); Irving W. and Charlotte F. Rabb Prize for Gastroenterology Research (2012); Dvorak Young Investigator Award for Health Services Research (2013); Journal Author Excellence Award, American Society for Healthcare Risk Management (2013); and the Nezam Afdhal Outstanding Achievement for Innovation in Gastroenterology Award (2015).

6. I received a Master's Degree in Nutrition at Columbia University in 1998 followed by an MD from the combined program though Columbia University and Ben Gurion University. I subsequently completed my internship and residency in Internal Medicine in 2005 and my fellowship in gastroenterology in 2008, all at Beth Israel Deaconess Medical

Center in Boston. I was supported by an NIH clinical investigator career development award from 2009-2014.

7. I have been asked to review the scientific literature and certain adverse event information in the possession of the defendants in these cases, to determine whether olmesartan can cause inflammation and damage to the small intestine resulting in malabsorption, diarrhea, abdominal pain, weight loss, vomiting and related symptoms. Relevant to this, I have cared for patients with severe malabsorption due to olmesartan induced inflammation in the lining of the small intestine, referred to below as “olmesartan enteropathy” but also previously known as “sprue-like enteropathy.” “Enteropathy” is the preferred medical terminology for pathologic changes in the lining (mucosa) of the small intestine. The term “sprue” was historically used to denote poorly understood intestinal disorders, but lacks a concrete medical definition. As the link between olmesartan and enteropathy has become accepted, “olmesartan enteropathy” has largely replaced “sprue-like enteropathy” in the medical literature. Olmesartan enteropathy, in my practice, was often misdiagnosed as one or a combination of celiac disease, refractory celiac disease, inflammatory bowel disease, collagenous colitis, microscopic colitis, lymphocytic colitis, autoimmune enteropathy or irritable bowel syndrome. The severity of symptoms I have observed in clinical practice range from chronic diarrhea and abdominal pain without weight loss, to severe malabsorption requiring multiple hospitalizations, and in one case cardiac arrest due to dehydration and electrolyte disturbances from severe diarrhea. All of the patients I have treated have had resolution of clinical malabsorption after cessation of olmesartan. In particular, looking back at a publication from my research group on refractory celiac disease, two patients were on olmesartan and likely had olmesartan enteropathy rather

than true refractory celiac disease and one of these patients eventually had olmesartan stopped, after which her gastrointestinal disease resolved, the second patient was lost to follow up.

8. I express each opinion to a reasonable degree of medical certainty. In making these determinations, I have followed the same procedures that I employ in my clinical practice. I have also used the same procedures that I employ in the clinical study of celiac disease and related gastrointestinal diseases.

II. RELATIONSHIP BETWEEN SMALL INTESTINAL INFLAMMATION, GASTROINTESTINAL SYMPTOMS AND MALABSORPTION

9. The normal small intestine is lined with tiny fingerlike projections called “villi.” Villi dramatically increase the absorptive surface area of the small intestine and produce many enzymes necessary for digestion. Between the villi are pit-like “crypts” which are responsible for regenerating damaged villi. In the normal intestine the villi are approximately 4 times the length of the crypts. As the intestine is damaged, the villi become shorter and the crypts become deeper as they hypertrophy to maintain sufficient villous structure. The healthy intestinal lining also contains all types of inflammatory cells at low numbers. The most prevalent inflammatory cell in the small intestine is the lymphocyte, often referred to as the “intra-epithelial lymphocyte” or IEL. A picture of normal intestinal lining can be seen in Figure 1.

10. Inflammation of the small intestine can be caused by immune mediated diseases such as celiac disease or Crohn’s disease, allergic/eosinophilic conditions, infections such as giardia or norovirus, immune deficiency syndromes such as Common Variable Immune Deficiency, and drugs including olmesartan. Histologic characteristics of small intestinal inflammation, also known as enteropathy, can include one or more of the following features: 1) increase in intraepithelial lymphocytes, 2) architectural disruption of the lining of the small

intestine with shortening, blunting or atrophy of villi, 3) lengthening of crypts between villi, 4) increase in subepithelial collagen deposition, 5) neutrophil infiltration with or without crypt abscesses or granulomas, 6) loss of goblet and paneth cells, and 7) increased eosinophils. These changes are not mutually exclusive; patients will often have more than one of these findings, and changes may be similar across different diseases. Changes are sometimes patchy in nature with areas of severely affected intestine in close proximity to areas which are normal or near normal. This patchy nature of inflammation occurs across many immune mediated disorders both inside and outside of the gastrointestinal tract.¹ A picture of damaged intestinal lining can be seen in Figure 2.

11. The diagnosis of olmesartan enteropathy is currently made clinically based on the presence of typical gastrointestinal symptoms and signs of malabsorption in patients taking olmesartan. Biopsy of the small intestine is not necessary if the presentation is typical for olmesartan enteropathy and the patient responds to olmesartan cessation. However, biopsy can be helpful in ruling out other disorders or to confirm response to withdrawal of olmesartan. While biopsies of the small intestine may diagnose enteropathy, biopsies are able to evaluate less than one 10,000th of the lining of the small intestine and we are unable to quantify the overall burden of damage over the entire intestine. This is one reason why the degree of enteropathy on biopsy is often not well correlated with severity of signs and symptoms of disease, and biopsy abnormalities can be minimal or non-existent, even in cases of clinically apparent olmesartan enteropathy, due to patchiness of disease.^{2,3} Lack of awareness by doctors about olmesartan enteropathy may delay evaluation and diagnosis, as may the presence of only mild to moderate symptoms. Some studies suggest that patients without severe symptoms or

severe enteropathy on biopsy are still at risk for complications of malabsorption, including anemia, osteoporosis and complications of chronic inflammation including lymphoma.^{4,5,6,7,8}

12. As the relationship between olmesartan and gastrointestinal symptoms and malabsorption has become more established, my current medical treatment is discontinuation of olmesartan and clinical observation. If patients do not respond to withdrawal of olmesartan, then further evaluation including endoscopy should be considered. This approach was recently set forth in the international 'Bucharest Consensus on Microscopic Enteritis'.⁴

13. Some adults with olmesartan enteropathy will be symptomatic without malabsorption. These individuals may have a range of symptoms including bloating, abdominal pain, vomiting, diarrhea, nausea, constipation, fecal incontinence and fatigue. These symptoms may wax and wane or be progressive over time, and are often attributed to irritable bowel syndrome before olmesartan enteropathy is diagnosed.

14. Other patients with olmesartan enteropathy will progress to malabsorption, defined as lack of proper absorption of food in the small intestine. Malabsorption can be caused by deficiencies in digestion, as with pancreatic exocrine insufficiency, where there is a lack of necessary digestive enzymes, or by decreased absorption due to olmesartan enteropathy. Symptoms of malabsorption can be acute or chronic. Acute symptoms include diarrhea, steatorrhea (fat malabsorption), weight loss, neuropathy and weakness/fatigue, and acute signs and laboratory manifestations include weight loss, anemia, rashes, dry skin, hair loss, kidney or liver injury and osteoporosis. While some of these issues, such as diarrhea, generally resolve with cessation of olmesartan, adverse health effects of moderate to severe malnutrition may persist. Chronic health effects which may persist even after normalization of nutritional status include neuropathy, weakness and fatigue, kidney injury, liver injury from

TPN (intravenous nutritional support), irritable bowel syndrome, fecal incontinence, neuropathy and osteoporosis. Each of these health outcomes may be caused by one or more issue related to olmesartan enteropathy. For instance, diarrhea in these cases is caused by a combination of the osmotic effects of unabsorbed food as well as active secretion related to inflammation. Anemia may be related to one or more vitamin deficiencies including iron, B12 and folate as well as direct effects of chronic inflammation. Renal injury is related to low blood pressure as well as electrolyte deficiencies. Acute liver injury may be caused by malnutrition itself, while chronic liver injury is a common consequence of TPN. Neuropathy, hair and skin changes are generally directly related to nutritional deficiencies such as B12 and zinc. Osteoporosis can be related to systemic inflammation as well as vitamin D deficiency, and often will not improve in older adults once bone mass is lost.

15. Even after clinical malabsorption and malabsorptive symptoms including diarrhea resolve after cessation of olmesartan, gastrointestinal symptoms including chronic abdominal pain and altered bowel habits consistent with irritable bowel syndrome may persist for years, as is seen after acute gastrointestinal infections.⁹ This post-inflammatory irritable bowel syndrome is differentiated from enteropathy by the lack of malabsorption and, if done, normal intestinal biopsies. It is notable that all the symptoms and medical issues discussed above are directly related to the enteropathy and malabsorption.

16. In addition, there may be multiple severe complications of therapy for malnutrition. As mentioned above, TPN can lead to permanent liver damage, and can also lead to severe, life threatening infections. Hospitalization and the need for intravenous access for fluids, electrolytes and nutrition can increase the risk of blood stream infections and blood

clots. Medical treatment and the illness itself results in significant economic and social consequences with missed work, loss of livelihood and social isolation.

17. These issues are compounded by frequent misdiagnosis of celiac disease in patients with olmesartan enteropathy and prescription of a gluten free diet. The gluten free diet has been reported to be nutritionally deficient in several studies.^{10,11,12} Specific nutritional issues commonly found in the gluten free diet include weight gain related to high-calorie gluten free substitute foods, elevated homocystine related to lack of b vitamins, and low calcium and iron.^{10,13,14,15}

18. Quality of life is also significantly compromised, both by chronic gastrointestinal symptoms and, where celiac disease is misdiagnosed, by the burden of constant dietary restriction. A number of studies have reported a diminished quality of life associated with both celiac disease and the gluten free diet.^{16,17,18,19} Data overall confirm that diagnosis of celiac disease has a significant psychological impact and that anxiety and depression may be ongoing issues in patients with celiac disease, affecting treatment adherence and overall quality of life.¹⁹

19. In addition to the specific quality of life impact of celiac disease diagnosis, there are also clearly documented effects of chronic gastrointestinal symptoms on quality of life and social function.²⁰ The burden of chronic gastrointestinal symptoms can be quite severe, with quality of life in affected patients similar to those with end stage renal disease or diabetes mellitus.^{21,22}

20. Beyond these acute consequences of olmesartan enteropathy, there are also significant long term sequelae of malnutrition which can affect nearly every organ system. Complications commonly seen in malnutrition include:

Cardiovascular	Hypotension, mitral valve prolapse, arrhythmias, heart failure
Dermatologic	Dry skin, alopecia, lanugo hair, pruritus
Gastrointestinal	Constipation, delayed gastric emptying, hepatitis, dysphagia
Endocrine and metabolic	Amenorrhea, infertility, osteoporosis, thyroid and cortisol abnormalities, hypoglycemia
Hematologic	Pancytopenia (anemia, immune suppression, increased bruising and bleeding)
Neurologic	Cerebral atrophy
Pulmonary	Aspiration pneumonia, emphysema related to vomiting
Psychological	Depression, irritability, apathy

Table 1.^{22,23}

A few of the more common and clinically significant effects of malnutrition include bone disease and immune suppression. Malnutrition causes impaired immune response through a variety of mechanisms including decreased number and function of immune cells leading to infection.^{24,25} Poor nutrition also can impair gut barrier function and increase intestinal permeability, which can lead to infection, liver damage and constitutional symptoms.^{25, 26,27}

III. IMMUNOLOGY AND PATHOGENESIS OF OLMESARTAN ENTEROPATHY

21. Enteropathy results from an inflammatory process with several etiological triggers. Recruitment and activation of intra-epithelial lymphocytes is pivotal and it is likely there are etiology-specific factors with a unique pro-inflammatory cytokine profile and triggering antigens. Enteropathy in celiac disease appears to be the closest match for the changes seen with olmesartan and is the best-understood related disorder. Celiac disease and olmesartan enteropathy are similar in that both involve the following: 1) stimulation of antigen-presenting cells to mature and express increased co-stimulatory molecules; and 2) a key cytokine in both celiac disease and olmesartan enteropathy is interleukin-15.

22. IL-15 is a central mediator in the innate to adaptive immune pathway. IL-15 is present in the epithelium and submucosa of the intestine and acts on multiple cell types

though multiple mechanisms to cause inflammation.^{28,29} In the normal immune system TGF beta is an important regulator of immune surveillance and prevents autoimmunity through suppression of T helper cells and promotion of regulatory T cells. However, elevated levels of IL-15, as described in olmesartan enteropathy³⁰ as well as celiac disease, leads to loss of immune homeostasis.^{28,31,32} This can occur even in the presence of normal TGF beta levels, either through TGF beta independent mechanisms, or through disruption of TGF beta signaling.^{29,32}

23. Substantive differences between celiac disease and olmesartan enteropathy include the following: 1) in celiac disease, environmental triggers such as viruses, bacteria and possibly gluten itself activate antigen-presenting cells including dendritic cells and epithelial cells. In olmesartan enteropathy, permissive environmental triggers may in some cases trigger the onset of enteropathy which is not dependent on gluten. 2) In celiac disease, Transglutaminase 2 and gluten peptides form complexes, which B cells internalize and then present the complexes on the HLA-DQ2 or HLA-DQ8 molecules on their surface. These gluten-specific B cells can bind with gluten-specific CD4⁺ T cells and stimulate differentiation of B cells into plasma cells, which produce antibodies both to gluten peptides and to the self-protein Transglutaminase 2. In olmesartan enteropathy, there does not appear to be cross reactivity with Transglutaminase 2, and no subsequent production of anti-transglutaminase antibodies, as in celiac disease. Additionally, while there does appear to be an association between HLA DQ2/DQ8 and olmesartan enteropathy, this is not nearly as strong as in celiac disease. This suggests that, unlike celiac disease, olmesartan enteropathy is either not HLA-dependent or is able to bind to a wider range of HLA molecules.

24. To summarize, olmesartan causes an enteropathy which is pathologically highly similar to celiac disease and appears to share key mechanisms triggering an interleukin 15-mediated inflammatory response. At the same time, there are notable differences between celiac disease and olmesartan enteropathy, including dependence on Transglutaminase 2 and HLA DQ2/DQ8 in celiac disease but not olmesartan enteropathy. In clinical practice, olmesartan enteropathy rather than celiac disease is suggested by response to withdrawal of olmesartan and lack of response to a gluten free diet and may be supported by the absence of celiac disease serologies such as tTG and DGP, and testing negative for HLA DQ2/DQ8. Family and personal medical history can also be supportive as many patients with celiac disease have a personal and/or family history of celiac disease or other autoimmunity, where this is uncommon in patients with olmesartan enteropathy.

25. In my clinical work and research studies, I often assess the relationship between exposures (to foods, medications and infections), gastrointestinal symptoms, and endoscopic/pathologic findings. In determining a potential causal relationship, I frequently take into account the following factors³³:

- Is there a plausible biological mechanism for this adverse effect;
- Is there evidence of withdrawal and challenge effects such that the symptoms/enteropathy improve with removal of the suspected agent and relapse with repeat exposure;
- Is there a temporal or dose response relationship between the exposure and the symptoms/disorder;
- Is there a known relationship between the exposure and the symptoms/disorder, either in medical literature or on the drug label;
- Are there other likely alternative explanations for the adverse effect.

IV. OLMESARTAN CAUSES ENTEROPATHY

26. It is my opinion, held to a reasonable degree of medical certainty, that olmesartan causes enteropathy with related gastrointestinal symptoms and malabsorption. I base my opinion on the following evidence:

A. Plausible Biologic Mechanism

27. While studies into the pathogenesis of olmesartan enteropathy are ongoing, data suggest that the mechanism is similar to that of celiac disease.^{30,34,35} In olmesartan enteropathy, as with celiac disease, it is clear that there is a profound increase in cytotoxic CD8+ T cells, which together with granzyme B+ cells are the main mediators of damage to the intestinal epithelium. Olmesartan also appears to increase expression of IL15 and IL15R, which are key regulators of intestinal immune function.³⁰ Indeed, IL15 has been considered to be a 'master regulatory cytokine', and overexpression of IL15 promotes the initiation and perpetuation of destructive T cell responses as described above.³⁶ Additionally, it was shown that olmesartan, but not related medications telmisartan and losartan, increased production of interleukin 15 with subsequent increased numbers of local CD8+ T cells, and resulted in disruption of the tight junctions between enterocytes lining the intestine, consistent with this mechanism.³⁰

28. In addition to the documented direct effects of olmesartan on key lymphocytes and cytokines, across multiple case series, 68-92% of patients diagnosed with olmesartan enteropathy have been found to be HLA DQ2 or HLA DQ8 positive, compared to 30-40% of the general population and 99% of patients with celiac disease.^{3,37,38} While the HLA linkage is not as strong as with celiac disease, this, in combination with the fact that celiac disease is histologically highly similar to olmesartan enteropathy, suggests that there may be olmesartan-related compounds which bind with high affinity to certain HLA molecules and further

promote the inflammatory reaction described above. In this model, olmesartan has the innate ability to upregulate mediators of intestinal inflammation with variable penetrance facilitated by, but not reliant on, environmental, HLA and likely other genetic factors. This immune activation leads to the increase in intraepithelial lymphocytes and villous destruction seen in olmesartan enteropathy, and is generally distinct from the findings in allergic/eosinophilic disorders or Crohn's disease.

B. Evidence of Temporal Response, Withdrawal and Rechallenge Effects

29. As is expected with autoimmune conditions, there is significant variation in time to onset of olmesartan enteropathy, and overall risk increases with duration of use. As reported in a study of the French National Health Insurance claim database evaluating all adult patients initiating ARB or ACEI between 1 January 2007 and 31 December 2012, the risk of olmesartan enteropathy increases with duration of exposure to olmesartan.³⁹ This is the pattern expected of intestinal adverse reactions from medications. Either a cumulative dose effect which triggers olmesartan enteropathy or a second environmental trigger could explain these epidemiological findings. This need for a 'second hit,' where an individual is predisposed to an inflammatory condition but does not manifest it until the immune system is primed by a secondary stimuli such as infection or stress, is common in allergy and autoimmunity.^{40,41} The lack of differential risk of olmesartan enteropathy by daily dose suggests that all clinical regimens are above the threshold for reactivity. This is similar to celiac disease where the threshold for reaction to gluten is well below common daily intake such that the amount and timing and gluten exposure is not a clear risk factor for individual development of celiac disease.⁴¹

30. As confirmed by multiple published case reports and in my clinical practice, olmesartan enteropathy is characterized by positive dechallenge and rechallenge effects, a

pattern of great clinical significance for causation. Once olmesartan enteropathy is identified and olmesartan is withdrawn, there is gradual improvement in both symptoms and intestinal inflammation. The rate of improvement can vary between individuals such that some patients are markedly better within days of stopping olmesartan and others take weeks or even months to substantially improve. This variability in response to withdrawal is commonly seen in other gastrointestinal disorders including celiac disease and may, in part, relate to degree of nutritional compromise at diagnosis. Finally, when rechallenge is attempted, most reports note very quick recurrence of gastrointestinal symptoms, usually within hours or days of exposure. This is also highly consistent with celiac disease and is related to an immune system that is already primed to react against an antigen.⁴² The time course for the onset of olmesartan enteropathy, as well as the response to both withdrawal and rechallenge, are very consistent with what would be expected for an antigen-based immune mediated enteropathy.

V. ADVERSE EVENTS REPORTED TO DEFENDANTS PROVIDE EVIDENCE OF CAUSATION

31. As part of my review, I assessed Medwatch forms relating to gastrointestinal adverse events experienced by patients taking olmesartan. Overall, these reports are highly consistent with the cases reported in peer reviewed literature, with the exception that these reports were submitted as early as 2004, while the first clear description of olmesartan enteropathy appeared in the medical literature 8 years later in 2012.³⁸ It is also notable that many early cases as early as 2004 have medically severe outcomes including hospitalization and very convincing evidence of early recurrence of symptoms with rechallenge. My review of these MedWatch reports supports my conclusion that olmesartan causes enteropathy. In addition, I was asked by Dr. David A. Kessler on 11/01/2016, to review 62 Medwatch cases of potential olmesartan enteropathy, selected because they had at least one of the symptoms of diarrhea,

vomiting or celiac disease either in the coded preferred terms or in the narrative discussion, positive rechallenge data and a serious outcome. These criteria are ones I consider highly relevant to diagnosis of olmesartan enteropathy. I reviewed each of these reports, and based on the information available, I performed a differential diagnosis on each to rule out other plausible, alternative causes, and we discussed my review by telephone on 11/22/2016. In this discussion, I confirmed that 60 of these 62 identified cases were highly consistent with olmesartan enteropathy, both by clinical syndrome and response to olmesartan withdrawal and rechallenge. One of the cases was excluded because the clinical syndrome of constipation, intestinal obstruction and pancreatitis was inconsistent with olmesartan enteropathy. The second case was excluded because the very fast onset of symptoms, within one week of starting olmesartan, is unusual with olmesartan enteropathy. Below, I have summarized five cases which are representative of the collection as a whole.

- a) A 58 year old woman had been treated with Benicar HCT 40/25 from the winter of 2003. In April 2004 she developed severe diarrhea. She was diagnosed with giardia infection, however a course of metronidazole did not improve her symptoms and she was hospitalized for dehydration in late April 2004. She stopped the Benicar at that time and symptoms resolved. After initial cessation the patient reports taking Benicar 'once in a while' for increased blood pressure. On each occasion she became "violently ill with vomiting and diarrhea." Since the patient and her physician concluded that these symptoms were due to the Benicar, no further episodes were reported. (Case SU-2004-002638.)

- b) A 56 year old woman had been treated with olmesartan medoxomil as part of a clinical trial SE-866/44 (ROADMAP) starting on January 13, 2006. On November 1, 2006 the patient developed 'gastroenteritis' and hypokalemia. Olmesartan was discontinued on November 6, 2006 and the patient was hospitalized from November 17, 2006 to November 28, 2006 and symptoms were reported to have resolved by December 1, 2006. Gastrointestinal symptoms recurred when olmesartan was reintroduced on December 3, 2006 and continued until December 24, 2006 when the medication was again stopped. Records are incomplete but it also appears that the patient was hospitalized again in early December due to diarrhea, dehydration, hypokalemia and hypocalcemia, and it is noted that "Study medication was finally discontinued due to adverse events Diarrhea and Vomiting on December 30, 2006." This case is notable as it occurred in the closely monitored clinical trial setting and is both severe with multiple hospitalizations and has clear evidence of rechallenge. (Case SP-2006-003369.)
- c) A 65 year old man had been treated with Benicar HCT for an unknown duration for hypertension. In May of 2007, he began to develop diarrhea. An antibiotic was prescribed for suspected infection without effect on his symptoms. Diarrhea continued and he reported being hospitalized 14 or 15 times for dehydration in 2007, with most hospitalizations lasting 4-5 days. He also experienced a 70 pound weight loss during this period. Weight loss was severe enough to warrant treatment with the

immunosuppressant 6-mercaptopurine, Total Parenteral Nutrition (TPN) and a surgically placed gastric feeding tube during the course of the year. After approximately seven months of symptoms, he had an endoscopy which diagnosed him with "gluten intolerance," likely due to presence of small intestinal villous atrophy. All of his medications were stopped late in 2007 and he was placed on a gluten free diet. At this time the diarrhea, lethargy and weight loss began to resolve. In October 2008, while still on a gluten free diet, the Benicar was restarted with return of diarrhea and weight loss. These symptoms slowly improved after Benicar was again stopped. It is notable that this patient has been given the diagnosis of Type 2 Refractory Celiac Disease, a severe and morbid prognosis and at the time of report was maintained on a gluten free diet despite rechallenge strongly suggesting olmesartan enteropathy rather than celiac disease as the cause of his severe malabsorption. (Case DSU-2009-002638.)

- d) A 70 year old woman began taking olmesartan medoxomil for hypertension in 2005. On March 12, 2010 she developed nausea and vomiting. Later that month, on March 18, 2010 she presented to the emergency room for these symptoms and had an abdominal ultrasound which showed gallbladder sludge, a non-specific finding. She was admitted to the hospital at that time and was discharged 10 days later on March 28. She was then admitted to the hospital again for similar symptoms on April 7, 2010, during which time she had a cholecystectomy. Symptoms continued requiring placement of a central line and feeding

tube. Benicar was stopped and she was able to be discharged. A short time after discharge, Benicar was restarted on April 13, 2010. She was then hospitalized again from April 28 to May 3, 2010. While in hospital, Benicar was again discontinued and the patient was able to be discharged. After discharge the Benicar was restarted on May 7, 2010, after which symptoms returned. At that time the olmesartan was discontinued permanently and there has been no recurrence of gastrointestinal symptoms. In summary, this patient had recurrent hospitalizations and underwent surgery to remove her gallbladder for gastrointestinal symptoms which were related to olmesartan. (Case DSU-2010-02706.)

e) A 79 year old man had been treated with olmesartan starting in December of 2006. In November of 2009 he was diagnosed with clostridium difficile infection and was treated. In December, 2009, he began to experience weight loss and diarrhea. The patient underwent a very extensive evaluation for the etiology of these symptoms including exploratory laparotomy, PET scan, and CT scans. In the course of illness, and with 30 pounds unintentional weight loss, the patient's blood pressure became low and olmesartan was discontinued at an unclear point in time. Afterward it is noted that weight loss and diarrhea resolved by July of 2010, however when olmesartan was restarted in August 2010, diarrhea and vomiting recurred. Olmesartan was then discontinued and replaced with an alternate anti-hypertensive. (Case DSU-2012-02939.)

VI. THE MEDICAL LITERATURE PROVIDES EVIDENCE OF CAUSATION

32. The medical literature provides robust evidence that there is a causal connection between olmesartan and enteropathy with gastrointestinal symptoms and malabsorption. Different studies in a variety of populations have consistently found evidence of olmesartan related gastrointestinal toxicity.

33. The first reports of significant gastrointestinal disease in patients on olmesartan was in 2010 when Drs. Rubio-Tapia and Murray published a series of 30 patients with the rare disorder collagenous sprue and noted that about one third of the patients in this series were taking olmesartan.⁴³

34. In 2012 Drs. Rubio-Tapia and Murray published a follow up paper describing 22 patients seen between 2008 and 2011 with enteropathy and chronic diarrhea, all of whom were taking olmesartan, between 10 and 40 mg per day for 6 months to 7 years before onset of symptoms.³⁸ The patients experienced diarrhea for a median of 19 months prior to suspension of olmesartan and all experienced at least some weight loss with a median of 18 kg, range 2 kg to 57 kg. 64% of the cohort had required at least one hospitalization and four required total parenteral nutrition. Improvement or complete remission was observed in all patients after cessation of olmesartan and 17 of 18 patients with a follow up small intestinal biopsy had histologic improvement. For patient safety and ethical reasons, there was no protocol for olmesartan rechallenge, however four patients in this series did resume olmesartan, all of whom reported recurrence of symptoms consistent with those experienced before the olmesartan was stopped.

35. In response to this report an article was subsequently published in the same journal in which the gastrointestinal treatment related adverse effects of the large pivotal 'Randomized Olmesartan and Diabetes Microalbuminuria Prevention (ROADMAP) study'

were presented.⁴⁴ This was the largest randomized controlled trial of olmesartan and included 2232 participants on olmesartan and 2215 on placebo followed for a median of 3.2 years. This analysis found no difference in the rate of intestinal or abdominal discomfort associated treatment related adverse effects including diarrhea and abdominal pain. It is notable that the most objective of these adverse events, 'weight decrease' was seen more frequently with olmesartan, although this event did not reach statistical significance. It is not surprising that this olmesartan enteropathy was not observed in the ROADMAP study initially published in 2011, as this study was underpowered for this adverse event based on number of patients included and length of follow up, did not include analysis of gastrointestinal effects as a primary or secondary endpoint, and involved diabetic patients leading to potentially confounding effects.

36. A second letter responding to the 2012 paper by Drs. Rubio-Tapia and Murray reports a patient with significant enteropathy, but with only mild anemia and upper gastrointestinal symptoms including reflux. Drs. Rubio-Tapia and Murray respond by noting that many of the patients in their series also had upper gastrointestinal symptoms which responded to olmesartan withdrawal and that there is "a spectrum of severity in olmesartan-associated-enteropathy."⁴⁵

37. In 2013, more case reports were published documenting severe enteropathy and gastrointestinal illness in patients on olmesartan, all of whom achieved complete remission after cessation of this medication without further treatment.^{37,46,47,48,49}

38. These reports and others directly reported to the FDA prompted the FDA Drug Safety Communication on 7-3-2013 detailing the olmesartan label change to include "intestinal

problems (sprue-like enteropathy) linked to blood pressure medication olmesartan

medoxomil.”⁵⁰ This statement advised health professionals:

- “Tell your patients to contact you if they develop severe, chronic diarrhea with substantial weight loss while taking an olmesartan-containing product, even if it takes months to years for symptoms to develop.
- If a patient develops these symptoms during treatment with olmesartan, other etiologies, such as celiac disease, should be investigated. If no other etiology is identified, olmesartan should be discontinued and another antihypertensive treatment started.
- Symptoms of sprue-like enteropathy may develop months to years after starting olmesartan.”

Subsequent recommendations in the medical literature advised cessation of olmesartan in any patient with symptoms suggestive of enteropathy as an initial step, followed by further evaluation only if signs and symptoms do not remit.⁵¹

39. Also in 2013, a large series of 72 patients with enteropathy and blood tests negative for celiac disease was reported in a 10 year retrospective analysis of cases from a leading referral center.³⁷ In this series medication related enteropathy was the leading non-celiac diagnosis, making up 26% of cases and 16 of the 19 medication related enteropathy cases were patients on olmesartan. The remaining three cases were due to mycophenolate mofetil and methotrexate, both potent immunosuppressive medications. All cases had a clinical and/or histological response to cessation of olmesartan.

40. 2014 saw the publication of more than 30 articles on olmesartan enteropathy. The most notable of these was the publication in abstract form of a French nationwide cohort study, published in full in 2015.³⁹ This study made use of the French National Health Insurance claim database to evaluate all adult patients initiating ARB or ACEI between 1 January 2007 and 31 December 2012 with no prior hospitalization for intestinal malabsorption or treatment for celiac disease. A total of 4,552,130 patients initiating ARB or ACEI treatment

were included. A total of 4,546,680 patients corresponding to 9 129 149 person-years were included. In this cohort, 218 hospitalizations for intestinal malabsorption were observed. The overall rate was 5.6 per 100,000 person years in the olmesartan group compared to 2.4 per 100,000 person years in the ACEI group and 1.8 per 100,000 person years in the non-olmesartan ARB group. This difference was highly statistically significant ($p < 0.0001$). Additionally this study found that risk of hospitalizations for intestinal malabsorption increased significantly with time for the olmesartan cohort, from 2.65 hospitalizations per 100,000 person years with less than 1 year of exposure to 6.71 hospitalizations per 100,000 person years with 1-2 years of exposure to 8.86 hospitalizations per 100,000 person years with 2 or more years of exposure to olmesartan. In comparison, there was a trend to decreased risk with time for the ACEI and non-olmesartan ARB cohorts, in other words, only olmesartan was found to be associated with hospitalization for intestinal malabsorption. This is a very robust study demonstrating an increased risk of hospitalizations for intestinal malabsorption with olmesartan. At the same time, as it only looked at hospitalizations, it is very likely an underestimate as the authors note "it is unlikely that all cases of olmesartan-associated enteropathy were captured by hospital diagnoses of intestinal malabsorption and coeliac disease. It is likely that milder forms also exist."³⁹

41. Along with multiple other case reports of olmesartan enteropathy, a number of other more systematic studies of this condition were published in 2014.^{3,52,53,54,55,56,57,58,59,60,61,62,63,64,65,66,67,68,69,70}

- A study which surveyed French gastroenterologists for any suspected case of diarrhea related to ARB use reported 48 cases, of which 47 were associated with olmesartan and one was associated with irbesartan.⁵² Of these 48 cases, data was

available for 40 patients. Of these 40 patients, one was on irbesartan, one had normal duodenal biopsies, and two didn't have any biopsies, and thus were excluded from analysis, leaving 36 patients. Of these 36, 32 had documented enteropathy while four had significant malabsorption with diarrhea and dehydration but without enteropathy on biopsy and 31 patients required hospitalization. This series also reported 9 cases in which cessation of olmesartan led to remission of symptoms followed by recurrence of symptoms with resumption of olmesartan.

- A case control study done out of a single center looked back at 2088 patients undergoing EGD and 12,428 patients undergoing colonoscopy. This study did not find any association between patients on olmesartan and the reported symptom of diarrhea at the time of endoscopy, however only a total of 105 patients were exposed to olmesartan which as the authors note "small prevalence of use of olmesartan (0.7%-1%) among study patients, limiting the power of this analysis."⁵⁸
- A systematic review identified 11 publications totaling 54 patients, almost all of whom had diarrhea and weight loss on olmesartan. All patients' symptoms resolved upon discontinuation of this medication. Other common symptoms included fatigue (56%), nausea and vomiting (45%), and abdominal pain (37%). This study also noted that 98% of patents had villous atrophy on small intestinal biopsy, increased collagen in the small intestine was seen in 33% of patients, 45% were anemic and 39% had low albumin levels. 72% were positive for HLA DQ2 or DQ8 while celiac antibody tests were universally negative.³

- A study in which patients undergoing outpatient upper endoscopy for abdominal pain, 20 of whom were on olmesartan, 20 of whom were non-olmesartan ARBs and 40 of whom were not on any of these medications, were reviewed for enteropathy. This study found that 50% of patients on olmesartan had one or more features of enteropathy, compared to 20% of matched controls. Conversely, non-olmesartan ARBs had a similar frequency of enteropathy compared to matched controls. This study suggests that there is likely to be a spectrum of intestinal injury seen with olmesartan, much of which does not result in symptoms severe enough to require hospitalization.⁷⁰

42. Studies in 2015 continued to document further case reports and case series of olmesartan enteropathy, and in addition several further studies of the pathogenesis and histological presentation were published.^{2,30,34,35,39,70,71,72,73,74,75,76,77,78,79,80,81,82,83,84,85,86,87,88}

- A group from the Mayo Clinic comprised of many of the authors who initially reported on olmesartan enteropathy, published a study of the pathogenesis of this condition. This study utilized intestinal biopsies taken from patients with olmesartan enteropathy on and off of the medication to evaluate the immune mechanisms of olmesartan related inflammation. This paper demonstrates that epithelial cells respond to olmesartan acid by increasing the expression of IL-15 and disruption of the key tight junction protein ZO-1 with a related increase in cytotoxic CD8+ cells. They suggest that a potential unifying theory for olmesartan enteropathy is that patients in certain circumstances are unable to control the increased IL-15 expression induced by olmesartan medoxomil, and as a result develop enteropathy.³⁰

- A study from Sweden evaluated the link between angiotensin receptor blockers and enteropathy by linking nationwide histopathology data and the Swedish Prescribed Drug Register.⁸⁸ This study evaluated the risk of non-olmesartan angiotensin receptor blockers use and the risk of ACE inhibitor use in 2,933 individuals with enteropathy and 14,571 controls. The authors reported that there was no relationship between enteropathy and either ARB or ACE inhibitor use, a finding which suggests that olmesartan enteropathy is largely drug specific and not a class effect.
- A further paper looked at the histological spectrum of olmesartan enteropathy as described in the literature to date. The authors reported that 92 of 100 individuals (92%) had total or partial villous blunting while 5% had normal villous architecture. Increased IELs were reported in 61 of 100 biopsies and subepithelial collagen thickening was reported in 22 of 100 biopsies. Variable degrees of chronic inflammation, acute inflammation, and increased eosinophils can be seen. Importantly, microscopic involvement of parts of the gastrointestinal tract other than the duodenum may be seen. Findings may include ulcers, lymphocytic and/or collagenous gastritis and changes in the colon that can be mistaken for lymphocytic or collagenous colitis.²

43. 2016 saw more publications related to gastrointestinal side effects of olmesartan.^{89,90,91,92,93,94,95,96,97}

- A regional Spanish registry study reported on 20 patients with olmesartan enteropathy.⁹¹ In this cohort, 14 patients (87.5%) required hospitalization, three patients had inflammation of the stomach and ten had inflammation of the

colon. In addition, lupus like conditions developed in three of the patients with arthritis and high titer auto-antibodies including anti-nuclear antibody (ANA). This lupus-like condition resolved with the gastrointestinal symptoms after withdrawal of olmesartan.

- An intriguing paper from one of the top celiac disease groups in Europe also reported two cases of olmesartan enteropathy with onset after an acute infection.⁹⁰ This phenomenon of post-infectious onset of immune mediated disease has been documented in celiac disease, microscopic colitis as well as diseases outside the intestine including neurologic disease and kidney disease and supports the concept that olmesartan, under the right genetic and environmental pressures, can trigger a drug dependent immune mediated enteropathy.

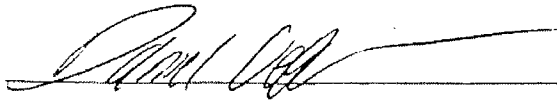
VII. SUMMARY OF MEDICAL LITERATURE REGARDING ASSOCIATION OF OLMESARTAN AND ENTEROPATHY

44. The medical literature addressed above provides strong evidence that olmesartan causes enteropathy of varying severity, with associated gastrointestinal symptoms which also may range from very severe requiring prolonged hospitalization and intravenous nutritional support, to relatively mild. Taken as a whole, the literature establishes a temporal relationship between duration of exposure to olmesartan and risk of enteropathy and intestinal malabsorption with significant variability in time to onset of olmesartan enteropathy. While no formal prospective studies of olmesartan rechallenge have been conducted, and are unlikely to be conducted due to ethical issues, numerous case reports attest that patients with olmesartan improve with cessation of this drug and relapse promptly if re-exposed to olmesartan. While understanding of the pathophysiology of olmesartan enteropathy is evolving, this appears to be

largely agent specific and does not involve other ARBs. Olmesartan enteropathy also appears to be an immune mediated phenomenon where olmesartan binds or otherwise upregulates IL15 and triggers CD8 mediated cytotoxicity.

45. Based on these data, my current clinical practice is to evaluate all patients presenting with gastrointestinal symptoms or signs of malabsorption for olmesartan or other potential causative agents. Olmesartan is discontinued at this time and if symptoms and malabsorption resolves, the diagnosis of olmesartan enteropathy can be made. There is no recommendation for rechallenge, or endoscopy to either confirm enteropathy or confirm resolution of enteropathy in patients with a clear and adequate clinical response. Alternatively, some patients are recognized to have enteropathy at endoscopy done for symptoms which have not been recognized to be potentially related to olmesartan enteropathy. All patients with a new diagnosis of enteropathy should be evaluated for olmesartan use and this medication discontinued when applicable. To proceed with extensive evaluation while continuing olmesartan places the patient at significant additional risk due to delay in instituting the definitive effective treatment of olmesartan withdrawal, as well as the risk and cost of unnecessary testing. My advice is noted in recent articles including in the conclusion of a recent review of olmesartan enteropathy in the *Annals of Internal Medicine*, "All patients should be warned to advise their physician and stop the drug if they develop any diarrhea or weight loss on olmesartan"⁸⁷ and in Cartee and Murray's *Sprue-like Enteropathy Associated with Olmesartan*, "It would seem reasonable to hold olmesartan much earlier in the natural history of the illness rather than assuming other diagnosis first in order to limit worsened symptoms leading to nutritional deficiencies and requiring a greater level of care and more extensive diagnostic evaluations."⁵¹

46. I reserve the right to supplement this expert report based on new information.

A handwritten signature in black ink, appearing to read "Paul J. DeLoe", is written over a horizontal line.

11-24-16
Date

FIGURE 1

Figure 1. Healthy Small Intestinal Lining
Photomicrograph and Illustration

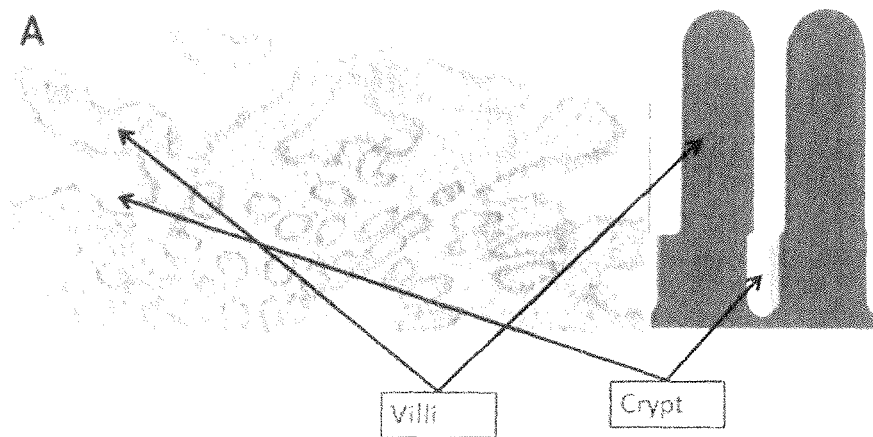
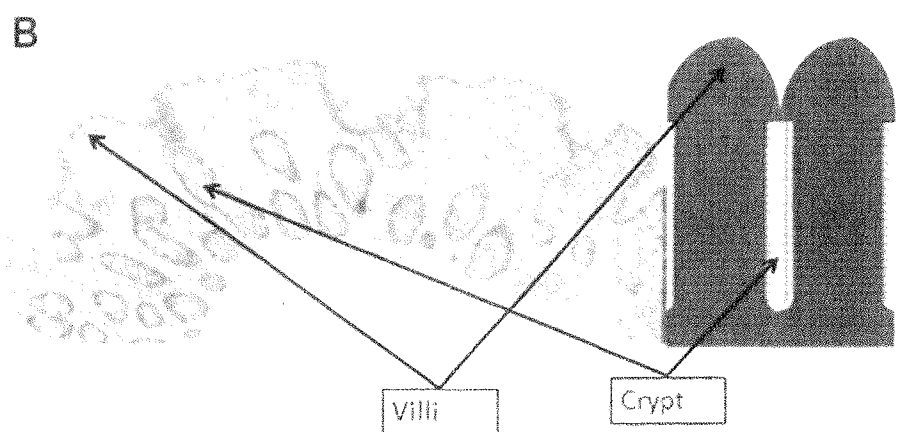


FIGURE 2

Figure 2. Small Intestinal Lining with Villous Atrophy/Enteropathy
Photomicrograph and Illustration



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2015 Fee Schedule and Contact Information For Medical Legal Case Reviewing

Daniel Leffler, MD, MS
Director of Quality Improvement
Research Director @ The Celliac Center
Division of Gastroenterology
Associate Director of Research and Quality
Department of Medicine
Beth Israel Deaconess Medical Center
Associate Professor of Medicine
Harvard Medical School

Address: 15 Clinton Place
Newton, MA 02459

Phone: 781-608-5918 (Home office)
617-667-1272 (BIDMC, Boston office)

Fax: 617-667-8144 (BIDMC, Boston)

Email: dleffler@bidmc.harvard.edu

Important Note: Please allow 2-4 weeks for completion of reviews.
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Fee Schedule: \$475 per hour for reviewing, report writing, and conferences

- 3 hour retainer fee prior to initiating review

\$750 per hour (or part thereof) for depositions

- 2 hour minimum, payable in advance

\$250 per hour plus expenses for travel to/from depositions or conferences

- 1 hour minimum

\$5,000.00 + expenses for court appearances
+ \$1500 per half day for additional travel/wait days

- Payable in full, 2 weeks in advance of the scheduled court date

Late cancellation fees (for events cancelled or postponed less than 14 days in advance of scheduled date)

- Depositions in Greater Boston area – \$1500.00
- Depositions outside Greater Boston - \$2,500.00

PRIOR TESTIMONY DURING THE PAST 3 YEARS

Ronda Orozco v. Boston Scientific Corporation d/b/a Mansfield Scientific Inc., Civil Action No.
MICV2012-03068, Superior Court, Middlesex

Deposition for Defendant

Daniel A. Leffler

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Harvard Medical School Curriculum Vitae

Date Prepared: 10/20/16
Name: Daniel Alexander Leffler, MD, MS
Office Address: Beth Israel Deaconess Medical Center
Dept. of Gastroenterology
330 Brookline Ave., E/Stoneman-385
Boston, MA 02215
Home Address: 15 Clinton Place
Newton, MA 02459
Work Phone: 617.667.1272
Work Email: dleffler@caregroup.harvard.edu
Work FAX: 617.667.8144
Place of Birth: Boston, Massachusetts

Education

09/92-06/96	B.S.	Biochemistry	Colorado College, CO
09/97-09/98	M.S.	Nutrition	Columbia University, NY
09/98-07/02	M.D.	Medicine	Ben Gurion University, Israel/ Columbia University, NY

Postdoctoral Training

07/02-06/03	Intern	Medicine	Beth Israel Deaconess Medical Center
07/03-06/05	Resident	Medicine	Beth Israel Deaconess Medical Center
07/05-06/06	Research Fellow	Gastroenterology	Beth Israel Deaconess Medical Center
07/06-06/08	Clinical Fellow	Gastroenterology	Beth Israel Deaconess Medical Center

Faculty Academic Appointments

07/08-05/09	Instructor	Medicine	Harvard Medical School
06/09-9/13	Assistant Professor	Medicine	Harvard Medical School
09/13-Present	Associate Professor	Medicine	Harvard Medical School

Appointments at Hospitals/Affiliated Institutions

07/08-present	Attending Physician Medicine (Gastroenterology)	Beth Israel Deaconess Medical Center
07/10-07/12	Research Specialist Physician	Fenway Community Health

Other Professional Positions

07/2016-present	Medical Director	Gastrointestinal Therapeutic Area	Takeda Pharmaceuticals
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Major Administrative Leadership Positions

Daniel A. Leffler

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Local

07/05-06/08	Clinical and Research Coordinator, Celiac Center	Beth Israel Deaconess Medical Center
07/08-Present	Director of Clinical Research, Celiac Center	Beth Israel Deaconess Medical Center
07/10-Present	Director, Celiac Center Clinical and Research Fellowship	Beth Israel Deaconess Medical Center
04/11-06/2016	Director of Quality Improvement, Division of Gastroenterology	Beth Israel Deaconess Medical Center
04/11-06/2016	Associate Director of Research for Quality Improvement, Department of Medicine	Beth Israel Deaconess Medical Center
07/12-06/2016	Clinical Research Director, Gastroenterology Fellowship Program	Beth Israel Deaconess Medical Center
08/12-06/2016	Course Co-Director, Patient Safety Core Faculty	Beth Israel Deaconess Medical Center
07/15-07/2016	Associate Firm Chief, Blumgart Firm	Beth Israel Deaconess Medical Center

Committee Service *(Member except where noted)*

Local

2008- 2016	Medical Peer Review Committee Department of Medicine	Beth Israel Deaconess Medical Center
2009-2016	Interventional Procedures Committee	Beth Israel Deaconess Medical Center
2009-2016	Gastrointestinal Hemorrhage Task Force	Beth Israel Deaconess Medical Center
2011-2016	Department of Medicine QI Leadership Council	Beth Israel Deaconess Medical Center
2012-2015	Colorectal Cancer Screening Advisory Committee	CRICO-Risk Management Foundation
2012-2016	Patient Safety Core Faculty, Department of Medicine	Beth Israel Deaconess Medical Center
2012-2016	Founding member of Center for Healthcare Delivery Sciences	Beth Israel Deaconess Medical Center
2014-2016	External Peer Review for Gastroenterology	Beth Israel Deaconess Network
2015-2016	Research Review Committee Center for Primary Care at Harvard Medical School	Harvard Medical School
2016	Poster Review Committee Soma Weiss Student Research Day	Harvard Medical School
2016-Present	Chairman; Colorectal Cancer Screening Advisory Committee	CRICO-Risk Management Foundation

National and International

2010-Present	Medical Advisory Board Healthy Villi Celiac Advocacy Group
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Daniel A. Leffler

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2010-Present	Medical Advisory Board Beyond Celiac (www.celiaccentral.org)
2010-2014	Collaborator/Founding Member Oslo Group on Standards and Definitions for Celiac Disease and Related Disorders
2012-2014	Secretary/Founding member North American Society for the Study of Celiac Disease (www.nasscd.org)
2013-Present	Medical Advisory Board Celiac Disease Foundation (www.celiac.org)
2013-Present	Digestive Diseases Week Abstract Review Committee American Gastroenterological Association
2014-Present	Scientific Grant Review Committee Italian Celiac Association 'Associazione Italiana Celiacia'
2014-2015	Steering Committee Member for the FDA Gastrointestinal Regulatory Endpoints and Advancement of Therapeutics Conference on Celiac Disease

Professional Societies (*Member except where noted*)

2005-Present	American Gastroenterological Association (AGA)
2005-Present	American College of Gastroenterology
2009-2011	AGA Press Advisory Board
2010-2016	Intestinal Diseases Section, AGA Institute Council
2010-Present	AGA Media Speakers' Bureau
2011-2015	AGA Academy of GI and Liver Educators Advisory Board
2016-Present	Councilor, AGA Institute, Intestinal Diseases Section

Editorial Activities

Ad hoc reviewer

- Alimentary Pharmacology and Therapeutics
- American Journal of Clinical Nutrition
- American Journal of Epidemiology
- American Journal of Gastroenterology
- American Journal of Physiology - Gastrointestinal and Liver Physiology
- Annals of Internal Medicine
- Annals of Neurology
- Appetite
- Archives of Internal Medicine
- British Medical Journal; Point-of-Care Physicians Reference Database
- British Journal of Nutrition
- Clinical Chemistry and Laboratory Medicine
- Clinical Infectious Diseases
- Diabetologia
- Digestive Diseases and Sciences

Daniel A. Leffler

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- European Journal of Clinical Investigation
- Expert Opinion on Drug Discovery
- Expert Review of Gastroenterology and Hepatology
- Gastroenterology
- Gastrointestinal Endoscopy
- Journal of Clinical Gastroenterology
- Journal of the American College of Nutrition
- Journal of the American Medical Association
- Journal of Medical Internet Research
- Journal of Pediatrics
- New England Journal of Medicine
- Therapeutic Advances in Gastroenterology

Other Editorial Roles

2010-Present	Editorial Board	Clinical Gastroenterology and Hepatology
2011-2013	Editorial Board	BMC Gastroenterology
2013-Present	Editorial Board	World Journal of Gastroenterology

Honors and Prizes

1994	Undergraduate Research Grant, Howard Hughes Institute
2006	Presidential Poster Award, American College of Gastroenterology
2006	AstraZeneca Senior Fellow Abstract Award, American College of Gastroenterology
2006	Program in Clinical Research Effectiveness, Harvard School of Public Health
2007	AstraZeneca Senior Fellow Abstract Award, American College of Gastroenterology
2010	PCIR Junior Investigator Laboratory Support Award, Harvard Catalyst
2012	Irving W. and Charlotte F. Rabb Prize for Gastroenterology Research
2013	Dvorak Young Investigator Award for Health Services Research
2013	Journal Author Excellence Award: American Society for Healthcare Risk Management
2015	Nezam Afdhal Outstanding Achievement in the Field of Excellence Award for Innovation in Gastroenterology

Teaching Awards

2008	Excellence in Tutoring Award, HMS Academy Center for Teaching and Learning
2010	Nominee, Excellence in Mentoring Award, HMS Office of Diversity and Community Partnership
2013	Nominee, Excellence in Mentoring Award, HMS Office of Diversity and Community Partnership
2014	Mentorship of Resident Research Award, Beth Israel Deaconess Medical Center

Report of Funded and Unfunded Projects

Daniel A. Leffler

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Past

- 2008-2010 Optimizing Safety in Ambulatory Procedural Care: Risk Informed Interventions (PI, Dierks, Meghan)
AHRQ R18 HS017907-01
Co-Investigator
My role was to provide guidance on risk areas in gastrointestinal endoscopy and assist with program design and evaluation including statistical methodology.
- 2006-2010 Assessing Gluten Free Diet Adherence in Adults with Celiac Disease (PI, Kelly, Ciaran)
Celiac Sprue Association
Co-Investigator
Major goal: to develop ways to measure dietary adherence in celiac disease as well as patient reported outcomes assessing symptoms and quality of life. I was responsible for study design, patient recruitment, statistical assessment and publication of results.
- 2008-2010 Development of a Long Term Follow-Up Alerting System for Integration into Electronic Medical Records (PI, Aronson, Mark)
CRICO/Risk Management Foundation
Co-Investigator
Major goal: to develop a framework for integrating reminder systems for patients needing repeat testing in the more distant future (>1 year). I was responsible for program design, evaluation, running patient and physician focus groups, liaising with IT specialists and assessing system performance.
- 2008-2010 Unrestricted Research Grant to Evaluate Clinical Outcomes in Celiac Disease
Alvine Pharmaceuticals (PI, Kelly, Ciaran)
Co-Investigator
Major goal: to develop and validate much needed non-invasive measures of celiac disease activity. I was responsible for study design, execution and evaluation.
- 2009-2010 Schwartz Center Connections (PI, Stanzler, Marjorie)
Schwartz Center and CRICO-RMF
Co-Investigator
Major goal: Working with a multi-disciplinary team led by the Schwartz Center and CRICO-RMF, this project aimed to identify and codify communication pathways between healthcare providers. Specific attention was paid to issues leading to miscommunication and adverse patient outcomes.
- 2008-2010 Eliminating Healthcare Disparities through Education: A Universal Medical School Program (PI, Shields, Helen)
Interfaculty Collaboration of Harvard Medical School, Harvard Business School and Harvard Graduate School of Education
Co-Investigator
Major Goal: To create a model for reducing health care disparities through the development of a longitudinal, integrated, tested educational program across all four years of medical school.
- 2011-2013 Clinical Utility of HLA Typing in Suspected Celiac Disease
Prometheus Laboratories
PI
Major goal: to evaluate use of HLA testing in celiac disease and to provide evidence-based guidelines for HLA testing and interpretation of results.
- 2012-2013 Evaluation of Mesalamine's Therapeutic Potential in Celiac Disease

Daniel A. Leffler

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Shire Pharmaceuticals

PI (\$111,129)

Major goal: to evaluate the in vitro efficacy of mesalamine to reduce celiac disease related intestinal inflammation

- 2009-2014 Biomarkers of Celiac Disease Activity During Gluten Challenge
NIH K23 DK082619
PI (\$931,230)
Major goal: As PI on this 5-year Mentored Patient-Oriented Research Career Development Award, our goal is to develop patient reported outcomes and non-invasive biologic markers to evaluate celiac disease activity.
- 2009-2014 Campaign to Improve Awareness of Celiac Disease Among Primary Care Physicians (PI, Kelly, Ciaran)
Sydney E. Frank Foundation
Co-Investigator (\$250,000)
Major goal: to develop tools to increase awareness and diagnosis rates of celiac disease in primary care practices. I assist with study design, content of informational module, and assessment of intervention efficacy.
- 2013-2014 Moderate Sedation – the final frontier for quality in procedural areas. - A multidisciplinary team based approach towards continuous improvement.
BIDMC Center for Healthcare Delivery
Co-Principal Investigator (\$42,000)
Major goal: to address the lack of moderate sedation benchmarks and to ensure that our patients can expect the safest and highest quality moderate sedation possible, and to monitor the effects of medication shortages and compare the costs and benefits of anesthesia administered deep sedation.
- Current**
- 2013-2015 Validation of Peripheral Microparticles as Novel Biomarkers of Celiac Disease Activity
NIH R03DK095937
PI (\$100,000)
Major Goal: The identify accurate non-invasive measures of celiac disease activity, which would be of great value in clinical practice, are prerequisite to the testing of new treatment modalities, and may offer insight into disease pathogenesis
- 2013-2015 Referral Management
CRICO-RMF
Co-investigator.(\$393,988)
Major Goal: The aim of this project is to develop and pilot systems for improved monitoring of patient referrals with the goals of improving adherence and reducing medical-legal consequences.
- 2014-2017 Measuring and Improving Colonoscopy Quality Using Natural Language
NIH-R01CA168959-04
Co-Investigator (\$905,880)
Major Goal: To develop a natural language processing system to automate assessment of colonoscopy quality and to use these data to evaluate physician factors which influence quality and assess the ability of performance metrics to lead to quality improvements.

Pending Risk & Outcomes from Screening & Treating Celiac Disease in T1D Adults: an RCT
NIH R01DK107857-01
PI (\$1,949,080)
Major Goal: This prospective, randomized controlled trial will provide rigorous data on the potential benefits of screening adults with T1D for celiac disease in the United States and on the outcomes associated with celiac disease screening initiatives on which to base health policy and medical guidelines.

Current Unfunded Projects

2008-Present Timing of Colonoscopy and Polyp Detection Rate is a project that assesses the influence of time of day in polyp detection to assess for endoscopist fatigue similar to what has been shown in surgical literature. (Co-investigator)

2008-Present Outcomes of Complicated Celiac Disease is a project to assess outcomes and medication usage of patients with non-responsive celiac disease, refractory celiac disease and celiac crisis. (Co-investigator)

Report of Local Teaching and Training

Teaching of Students in Courses

2005 Examiner, Objective Structured Clinical Exam Training
Harvard Medical Exchange Students
Harvard Medical School
3 hrs. contact time

2005 Fourth Year Medical Student Clinical Skills Tutorial
HMS Medical Students
Harvard Medical School
6 hrs. contact time

2005-2008 Tutor, Gastrointestinal Pathophysiology Course 708.0 *Human Systems/Module IIA*
HMS medical students
Harvard Medical School
Three, 2-hr. sessions per week for 4 weeks

2006-2012 Board review Sessions, Gastrointestinal Pathophysiology 708.0, *Human Systems/Module IIA*
HMS medical students
Harvard Medical School
2, 1-hr. sessions per year

2009-Present Pathology Lab Co-Instructor, Gastrointestinal Pathophysiology 708.0, *Human Systems/Module IIA*
HMS medical students
Harvard Medical School
Three, 2-hr. sessions per week for 4 weeks

Formal Teaching of Residents, Clinical Fellows and Research Fellows (post-docs)

2007, 2010, Update on Celiac Disease
2013 Medical Interns and residents

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- Beth Israel Deaconess Medical Center
1 hr. lecture
- 2007-Present Advanced Diagnosis and Management of Celiac Disease
15 Clinical Gastroenterology Fellows
Beth Israel Deaconess Medical Center
1-hr didactic sessions, annually
- 2012-Present Annual Fellows QI and Safety Symposium
40 Clinical Medicine fellows (all subspecialties)
Beth Israel Deaconess Medical Center
3-hr didactic sessions, 4 x annually

Clinical Supervisory and Training Responsibilities

- 2008-Present Consult Attending in Gastroenterology, Beth Israel Deaconess Medical Center
4 weeks per year, 3-4 hours per day
- 2008-Present Endoscopy Training for Fellows, Beth Israel Deaconess Medical Center
One day per month, 8 hours per day
- 2012-Present Ad hoc guidance for senior medical residents and gastroenterology fellows working on quality improvement and patient safety projects.

Laboratory and Other Research Supervisory and Training Responsibilities

- 2006-Present Supervision of residents and research assistants working on clinical research projects.
- 2008-2013 I mentor medical residents at BIDMC in an ongoing case-control design project to assess the influence of ethnicity on risk and severity of Clostridium difficile infection.
- 2009-2013 I mentor medical residents at BIDMC on a survey based project to evaluate patient perceived burden of the gluten free diet in celiac disease in comparison to treatments for a variety of other medical conditions. This study will also assess the influence of socioeconomic status and educational level on burden of disease and reported treatment adherence.

Formally Supervised Trainees

- 2008-2009 **Shailaja Jamma, MD** / Research Fellow
Received a research award from the American College of Gastroenterology and published multiple abstracts and manuscripts. Completed gastroenterology fellowship at University of Chicago. Currently on staff at Gastrointestinal Care Consultants Houston, TX.
- 2010-2011 **Kumar Pallav, MD** / Celiac Clinical/Research Fellow
Supervised the planning and execution of multiple clinical research projects as well as patient care. Completed gastroenterology fellowship at University of Mississippi. Currently on faculty at University of Mississippi
- 2011-2013 **Toufik Kabbani, MD** / Celiac Clinical/Research Fellow
Supervised the planning and execution of multiple clinical and translational research projects, resulting in multiple published manuscripts and presentations at national meetings. Also formally supervised patient care activities. Currently in gastroenterology fellowship at University of Pittsburgh Medical Center
- 2012-2013 **Rohini Vanga, MD** / Celiac Clinical/Research Fellow
Supervised the planning and execution of multiple clinical and translational research projects. Also

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formally supervised patient care activities. Currently in gastroenterology fellowship at Baylor University

- 2013-2014 **Themaiah Theetira, MD** / Celiac Clinical/Research Fellow
Supervised the planning and execution of multiple clinical and translational research projects. Also formally supervised patient care activities. Currently in gastroenterology fellowship at University of California, Fresno
- 2014-2016 **Dharmesh Kaswala, MD** / Celiac Clinical/Research Fellow
Supervised the planning and execution of multiple clinical and translational research projects. Also formally supervised patient care activities. Starting gastroenterology fellowship at California Pacific Medical Center, July 2016
- 2014-2016 **Gopal Veeraghavan, MD** / Celiac Clinical/Research Fellow
Supervised the planning and execution of multiple clinical and translational research projects. Also formally supervised patient care activities. Starting gastroenterology fellowship at University of California, Fresno, July 2016
- 2015-2016 **Satya Kurada, MD** / Celiac Clinical/Research Fellow
Supervised the planning and execution of multiple clinical and translational research projects. Also formally supervised patient care activities.
- 2013-2015 **Adelina Hung, MD** BIDMC Medical Resident Supervised the planning and execution of multiple clinical and quality improvement projects. Currently in gastroenterology fellowship at Yale.
- 2014-2016 **Manida Wungjiranirun, MD** BIDMC Medical Resident. Supervised the planning and execution of multiple clinical and quality improvement projects. Starting gastroenterology fellowship at Brown University, July 2016
- 2015-2016 **Katherine Germansky, MD** BIDMC gastroenterology fellow. Supervised the planning and execution of multiple clinical and quality improvement projects. Starting on faculty at Beth Israel Deaconess Medical Center, July 2016.
- 2015-2016 **Sarah Shannahan, MD** BIDMC Medical Resident. Supervising celiac disease research projects and review articles.
- 2015-2016 **Laurie Grossberg, MD** BIDMC gastroenterology Fellow. Supervising quality improvement research projects looking at colonoscopy safety.

Local Invited Presentations *No presentations below were sponsored by outside entities*

- 2007-2009 Gastrointestinal Bleeding Module, Bedside Emergencies Conference
Clinical RNs
Beth Israel Deaconess Medical Center, Boston, MA (1-hr session, 3 x annually)
- 2010 Celiac Disease: A Modern Understanding of an Ancient Disease / Clinical Grand Rounds
Brigham and Woman's Hospital, Boston, MA
- 2010 Celiac Disease: Lessons from an Ancient Disorder / Gastroenterology Grand Rounds
Massachusetts General Hospital, Boston, MA
- 2011 Clinical Crossroads: Celiac Disease / Medical Grand Rounds
Beth Israel Deaconess Medical Center, Boston, MA
- 2011 Celiac Disease: The Usual and Unusual
Brigham Update in Medicine - Partners Healthcare
Boston, Ma
- 2011 Celiac Disease: Modern Lessons From an Ancient Disease

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- Updates in Gastroenterology Lecture series
Beth Israel Deaconess Medical Center, Boston, Ma
- 2011, 2012

Cross-Cultural Care in the Pre-Clinical Years / Use of Case Triggers and Vignette Writing
Healing Health Care Disparities through Education: An Interactive Faculty Development Program,
Harvard Medical School, Boston, MA
- 2011

Update in Celiac Disease / Allergy/Immunology Grand Rounds
Massachusetts General Hospital, Boston, MA
- 2011

Celiac Disease and Infertility / Grand rounds
Boston IVF / Division of Reproductive Endocrinology and Infertility
Beth Israel Deaconess Medical Center, Boston, MA
- 2011

Celiac Disease: Modern Lessons From an Ancient Disease / Grand Rounds
Beth Israel Deaconess Needham, Needham, MA
- 2012

Celiac Disease: Modern Lessons From an Ancient Disease / Rheumatology Grand Rounds
Brigham and Women's Hospital, Boston, MA
- 2012

Celiac Disease: Update for PCPs
Meet the Professor
Office Practice of Primary Care Medicine Symposium
Brigham and Women's Hospital, Boston, MA
- 2012

Celiac Disease: Modern Lessons From an Ancient Disease / Grand Rounds
Joslin Diabetes Center, Boston, MA
- 2012

Celiac Disease: Endocrine Aspects / Endocrinology Grand Rounds
Children's Hospital Boston, Boston, MA
- 2013

Celiac Disease: Lessons from the Adult World / Gastroenterology Grand Rounds
Children's Hospital Boston, Boston, MA
- 2014

Course Director: Academic Achievement in Quality Improvement. Beth Israel Deaconess
Medical Center, Boston, MA

Report of Regional, National and International Invited Teaching and Presentations

Invited Presentations and Courses

Regional *Those presentations below sponsored by outside entities are so noted and the sponsor is identified*

- 2008

Celiac Disease Update / Invited speaker
A Core Curriculum In Primary Care Medicine
Boston University School of Medicine
- 2009

The Modern Face of Celiac Disease / Invited Keynote speaker
New England Society of Gastroenterology Nurses and Associates (NESGNA)
Annual Educational Conference, Boston, MA
- 2010

An Update on Celiac Disease Diagnosis and Treatment / Medical Grand Rounds
Sturdy Memorial Hospital
Attleboro, Ma
- 2012

Celiac Disease: Protean Manifestations/Invited speaker
Update in Internal Medicine, Beth Israel Deaconess Medical Center
Boston, MA
- 2014

Celiac Disease
Gastroenterology Grand Rounds Massachusetts General Hospital
Boston, MA

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- 2014 Update on Celiac Disease
Harvard University Health Services
Boston, MA
- 2015 Review of Gastroenterology / Course instructor
ACP Review Course
American College of Physicians
Boston, MA
- 2015 Colorectal Cancer Screening: Current Recommendations and Controversies
Best Practices
CRICO-RMF
Boston, MA
- 2016 Celiac Disease and Gluten Sensitivity: Similarities and Differences
Update in Internal Medicine, Beth Israel Deaconess Medical Center
Boston, MA

National *Those presentations below sponsored by outside entities are so noted and the sponsor is identified*

- 2008 Patient Reported Outcomes in Celiac Disease / Invited speaker
Clinical Trial Outcomes in Celiac Disease (Alba Pharmaceuticals)
New York City
- 2009 Meeting the Needs of Adults with Celiac Disease / Invited speaker
Food and Nutrition Conference and Expo
American Dietetic Association
Denver, CO
- 2009 Safety, Tolerability and Effects On Intestinal Permeability of Larazotide Acetate in Celiac Disease:
Results of a Phase IIB 6-Week Gluten-Challenge Clinical Trial (Abstract)
Digestive Diseases Week, American Gastroenterological Association
Chicago, IL
- 2010 Quality of Life and Patient Reported Outcomes in Celiac Disease / Invited speaker
Development of Therapies for Celiac Disease
Columbia University
New York City
- 2010 1) Focused Clinical Update: Celiac Disease / Invited speaker
2) Meet the Professor Lunch: Refractory Celiac Disease and Diet Adherence
3) An Update on Celiac Disease Diagnosis and Treatment / Session Chair
4) Diagnosis and Highly Effective Medical Management of Celiac Disease / Session Chair
Digestive Diseases Week, American Gastroenterological Association
New Orleans, LA
- 2010 An Update on Celiac Disease Diagnosis and Treatment / Invited speaker
Medical and Surgical Advances in Gastroenterology
Lee Memorial Health System, Fort Meyers, FL
- 2010 Celiac Disease: Protean Manifestations / Invited speaker
PRIMED Update in Primary Care (PRIMED)
Boston, MA
- 2011 Refractory Celiac Disease Research Forum / Session Chair
Digestive Diseases Week, American Gastroenterological Association
Chicago, IL

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- 2011 1) Celiac Disease: Protean Manifestations / Invited speaker
 2) Clostridium Difficile Infection: Not Just a Hospital Problem / Invited speaker
 PRIMED Update in Primary Care (PRIMED)
 Anaheim, CA
- 2011 Celiac Disease: Important and Often Missed / Invited speaker
 Author in the Room, IHI/JAMA
 Boston, MA
- 2011 PROs for Celiac Disease: Measuring What Patients Care About / Gastroenterology Grand Rounds
 Columbia University, NYC
- 2012 Celiac Disease: Modern Lessons From an Ancient Disease / Grand Rounds
 Pinnacle Health System/Harrisburg Hospital
 Harrisburg, PA
- 2012 1) Clostridium Difficile Infection: Not Just a Hospital Problem / Invited speaker
 2) Celiac Disease: Protean Manifestations / Invited speaker
 PRIMED Update in Primary Care (PRIMED)
 Fort Lauderdale, FL
- 2012 AGA Academy of Educators Plenary Session/ Invited speaker
 Digestive Diseases Week, American Gastroenterological Association
 San Diego, CA
- 2012 Review of Gastroenterology / Course instructor
 ACP Review Course
 American College of Physicians
 Boston, MA
- 2012 Gastroenterology Ask the Expert
 PRIMED Update in Primary Care (PRIMED)
 Boston, MA
- 2013 Visiting Professor/Gastroenterology Grand Rounds
 Northwestern Medical Center
 Chicago, IL
- 2013 Review of Gastroenterology / Course instructor
 ACP Review Course
 American College of Physicians
 San Francisco, CA
- 2013 1) Celiac Disease: Protean Manifestations / Invited speaker
 2) Chronic Diarrhea: A Practical Approach / Invited speaker
 PRIMED Update in Primary Care (PRIMED)
 Anaheim, CA
- 2013 Update on Colorectal Cancer Screening
 Gastroenterology and Hepatology Academy
 Virtual Symposium
- 2013 Advances in Celiac Disease Diagnosis / Session Chair
 Digestive Diseases Week, American Gastroenterological Association
 San Diego, CA
- 2013 The True Burden of Celiac Disease: Making the Case for Prevention / Invited Speaker
 Digestive Diseases Week, American Gastroenterological Association
 San Diego, CA

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- 2013 Celiac Disease: Presentation and Diagnosis from a Clinical and Pathologic Perspective /
Invited Speaker
Digestive Diseases Week, American Gastroenterological Association
San Diego, CA
- 2013 Small Bowel Disease Board Review Session / Invited Speaker
Digestive Diseases Week, American Gastroenterological Association
San Diego, CA
- 2013 Diagnosing Celiac Disease in 2013/Invited Speaker
13th International Celiac Disease Symposium
Chicago, IL
- 2013 Review of Gastroenterology / Course instructor
ACP Review Course
American College of Physicians
Boston, MA
- 2013 1) Celiac Disease: Protean Manifestations / Invited speaker
2) Clostridium Difficile Infection / Invited speaker
PRIMED Update in Primary Care (PRIMED)
Boston, MA
- 2014 Measuring Outcomes in Celiac Disease / Invited Speaker
Developing Therapies for Celiac Disease Conference
New York, NY
- 2014 Celiac Disease/ Invited speaker
PRIMED Update in Primary Care (PRIMED)
Phoenix, AZ
- 2014 Celiac Disease/ Invited speaker
PRIMED Update in Primary Care (PRIMED)
Seattle, WA
- 2014 Celiac Disease/ Invited speaker
PRIMED Update in Primary Care (PRIMED)
Denver, CO
- 2014 Celiac Disease/ Invited speaker
PRIMED Update in Primary Care (PRIMED)
Houston, TX
- 2014 Celiac Disease/ Invited speaker
PRIMED Update in Primary Care (PRIMED)
Chicago, IL
- 2014 Small Bowel Disease Board Review Session / Invited Speaker
Digestive Diseases Week, American Gastroenterological Association
Chicago, IL
- 2014 Celiac Disease Who to Screen, How to Test and Diagnose?/Invited Speaker
Digestive Diseases Week, American Gastroenterological Association
Chicago, IL
- 2014 Update on Celiac Disease/Invited Speaker
University of Colorado Medical Center Gastroenterology Grand Rounds

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- 2014 Celiac Disease and Non Celiac Gluten Sensitivity / Invited Speaker
University of Colorado Medical Center Updates in Clinical Nutrition
- 2015 Role of Serology to Measure Clinical Benefit and Appropriate timing of assessment in Celiac
Disease / Invited Speaker
FDA Gastrointestinal Regulatory Endpoints and Advancement of Therapeutics Conference on
Celiac Disease
- 2015 Small Bowel Disease Board Review Session / Invited Speaker
Digestive Diseases Week, American Gastroenterological Association
Washington DC
- 2015 Celiac Disease Clinical Research Abstract Session/Invited Speaker
Digestive Diseases Week, American Gastroenterological Association
Washington DC
- 2015 Celiac Disease Factors Influencing Development of Disease/Session Moderator
Digestive Diseases Week, American Gastroenterological Association
Washington DC
- 2015 Celiac Disease: Protean Manifestations / Invited speaker
PRIMED Update in Primary Care (PRIMED)
Boston, MA
- 2016 Celiac Disease
Grand Rounds, Norwalk Hospital, Norwalk, CT
- 2016 Small Bowel Disease Board Review Session / Invited Speaker
Digestive Diseases Week, American Gastroenterological Association
San Diego, CA
- 2016 New Therapeutic Approaches in Celiac Disease /Session Moderator
Digestive Diseases Week, American Gastroenterological Association
San Diego, CA
- 2016 'Help my gluten free diet isn't working!' Postgraduate course Invited Speaker
Digestive Diseases Week, American Gastroenterological Association
San Diego, CA
- 2016 New Developments in Celiac Disease Research Session/Invites Speaker
Digestive Diseases Week, American Gastroenterological Association
San Diego, CA
- 2016 Celiac Disease: Below the Tip of the Iceberg. Invited Speaker, ImmunosanT Sponsored
Symposium. San Diego, CA

International *Those presentations below sponsored by outside entities are so noted and the sponsor is identified*

- 2007 Psychological correlates of gluten-free diet adherence / Invited speaker (Abstract)
International Celiac Disease Society / 21st Annual Association of European Celiac Societies
Meeting, Maribor, Slovenia
- 2011 The Future of Celiac Disease / Keynote address
Canadian Celiac Association Annual Celiac Conference
Ottawa, Canada
- 2011
 - 1) Monitoring of Individuals with Celiac Disease: Knowns and Unknowns / Clinical Forum
 - 2) Monitoring of Individuals with Celiac Disease: Knowns and Unknowns / Scientific
Symposium

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	International Celiac Disease Society 14 th International Celiac Symposium Oslo, Norway
2012	Clinical Dilemmas in Celiac Disease / Invited speaker XII Congress of the Russian Scientific Society of Gastroenterology Moscow, Russia
2012	Celiac Disease: Modern Lessons From an Ancient Disease / Nutrition and Metabolism Workshop Palliser Primary Care Network Calgary, Ontario, Canada
2013	Celiac Disease and Cardiovascular Outcomes University of Orebro Orebro, Sweden
2014	Celiac Disease City Wide Gastroenterology Grand Rounds, University of Toronto Toronto, Canada
2014	Celiac Disease/ Plenary Session Alberta Digestive Disease Society Annual Meeting Calgary, Canada
2014	Serum Markers in Celiac Disease: Standards and Novel Approaches Dr. Falk, Small Bowel Symposium Amsterdam, Netherlands
2014	Non-Celiac Gluten Sensitivity vs. Celiac Disease: Diagnostic Approaches Third Non-Celiac Gluten Sensitivity Symposium Salerno, Italy
2015	Celiac Disease: Changes in Prevalence, Novel Diagnostics, Evaluation of Non Responsive Celiac Disease and Future Therapies Latin American Symposium on Celiac Disease/Course on Diseases of the Intestine and Colon Buenos Aires, Argentina
2016	Novel Developments in Celiac Disease Therapeutics Autoimmunity 2016 Leipzig, Germany

Report of Clinical Activities and Innovations

Current Licensure and Certification

2005	Internal Medicine License
2005	Board Certified in Internal Medicine
2008	Board Certified in Gastroenterology

Practice Activities

Ambulatory Care	Outpatient Clinic	BIDMC	One session per week
Endoscopy	Endoscopy Unit	BIDMC	One session per week
Consult Attending	Inpatient Units	BIDMC	Four weeks per year

Clinical Innovations

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- 2008 Handheld ingredient scanner for detection of gluten containing foods.
I partnered with an electronics design firm to create and market a handheld device capable of scanning food barcodes to assess for foods known or suspected to contain gluten. The aim is to decrease the burden of gluten free diet adherence and thus improve gluten avoidance, especially in those with visual or literacy deficits who are most at risk for inadvertent gluten exposure.
- 2010 System for Improving Endoscopy Patient Recall
I led a team of gastroenterologists, primary care physicians and quality improvement specialists in a project to design, implement and study an automated system for improving patient adherence to follow up endoscopy recommendations. This work led to increased numbers of patients effectively managed for clinically significant conditions as well as peer reviewed publications and presentations at national meetings.
- 2012 Ex-Vivo Gluten Challenge for Diagnosis of Celiac Disease
I have developed a novel method of diagnosing celiac disease in patients already on a gluten challenge using ex-vivo gluten challenge in cultured intestinal biopsies. Work is ongoing to develop and protect this innovation which has the potential to be a widely used new tool for clinical and research activities in celiac disease and other gluten related disorders.

Report of Education of Patients and Service to the Community

Activities

- 2006-Present Healthy Villi Celiac Advocacy Group
Presented lectures on evolving topics in celiac disease and participated in question and answer session. Quarterly with attendance of ~400 per meeting.
- 2007-Present Celiac Center at BIDMC
Participate in design and execution of quarterly information sessions for patients with newly diagnosed celiac disease. Attendance ~30 per meeting
- 2008 Celiac Center at BIDMC
Participate in design and execution of a patient education forum for adults with celiac disease. Attendance ~200
- 2009 New England Celiac Conference
Participated with the Healthy Villi in planning and delivering content at this annual regional meeting. Attendance in 2009 was over 650 individuals.
- 2009-2012 Celiac Center at BIDMC and at Children's Hospital, Boston
Project leader for the development of an educational program for young adults with celiac disease as they plan to leave the home
- 2012-Present Regular guest contributor to the patient magazine *Gluten Free Living*
- 2014-Present Regular guest contributor to the patient magazine *Living Without*
- 2013 BIDMC Mini-Medical School Lecture: Food Related Disorders
Presenter

Educational Material for Patients and the Lay Community

Patient educational material

- 2007 Co-Author of Celiac Disease: A Primer
Patient education pamphlet

Available through the Divisions of Gastroenterology and Nutrition at BIDMC, >5,000 distributed

2010

Dennis M, **Leffler D**.

Real Life With Celiac Disease: Troubleshooting and Thriving Gluten Free

Book published by the American Gastroenterological Association

Winner of the 2011 'Indie Book Award' for Diet and Nutrition: www.indiebookawards.com

Currently sold >10,000 copies nationwide. Current rating on Amazon: 4.9 out of 5 stars

Report of Scholarship

Peer reviewed publications in print or other media

Research Investigations

1. **Leffler D**. U.S. high school age girls may be receptive to breastfeeding promotion. Journal of Human Lactation 2000;16(1):37-41
2. **Leffler D**, Dennis M, George J, Kelly CP. The Interaction Between Eating disorders and Celiac Disease: An Exploration of Ten Cases. Eur J Gastroenterol Hepatol. 2007 Mar;19(3):251-5.
3. **Leffler D**, Dennis M, Hyett B, Kelly E, Schuppan D, Kelly CP. Etiologies and Predictors of Diagnosis in Non-Responsive Celiac Disease. Clin Gastroenterol Hepatol. 2007 Apr;5(4):445-50
4. Shields HM, Guss D, Somers SC, Kerfoot BP, Mandell BS, Travassos WJ, Ullman SM, Maroo S, Honan JP, Raymond LW, Goldberg EM, **Leffler DA**, Hayward JN, Pelletier SR, Carbo AR, Fishman LN, Nath BJ, Cohn MA, Hafler JP. A Faculty Development Program to Train Tutors to Be Discussion Leaders Rather Than Facilitators. Acad Med. 2007 May;82(5):486-492.
5. **Leffler D**, Edwards-George J, Dennis M, Cook E, Schuppan D, Kelly C. A prospective comparative study of five measures of gluten free diet adherence in adults with celiac disease, Alimentary Pharmacology & Therapeutics. 2007 Nov 1;26(9):1227-35
6. **Leffler D**, Edwards-George J, Dennis M, Cook F, Schuppan D, Franko DL, Blom-Hoffman J, Kelly CP. Factors that influence adherence to the gluten-free diet in adults with celiac disease. Digestive Diseases and Sciences. 2008 Jun;53(6):1573-81.
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8. Shields HM, **Leffler D**, White A, Hafler J, Pelletier S, O'Farrell RP, Llerena-Quinn R, Hayward J, Salamone S, Lenco A, Blanco P, Peters A. Integration of Racial, Cultural, Ethnic and Socio-Economic Factors into a Gastrointestinal Pathophysiology Course. Clinical Gastroenterology and Hepatology. 2009 Mar;7(3):279-84.
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10. Garud S, **Leffler D**, Dennis M, Edwards-George J, Saryan D, Sheth S, Schuppan D, Jamma S, Kelly CP. Interaction between psychiatric and autoimmune disorders in celiac disease patients in the United States. Aliment Pharmacol Ther 2009 Apr 15;29(8):898-905.
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- and Hepatology. 2009 May;7(5):530-6, 536.e1-2.
12. Hyett B, Martinez F, Gill BM, Mehra S, Lembo A, Kelly CP, **Leffler DA**. Delayed Radionucleotide Gastric Emptying Studies Predict Morbidity in Diabetics with Symptoms of Gastroparesis. *Gastroenterology* 2009 Aug;137(2):445-52.
13. **Leffler DA**, Dennis M, Edwards George J, Jamma S, Cook E, Schuppan D, Kelly CP. A Validated Disease Specific Symptom Index for Adults with Celiac Disease. *Clinical Gastroenterology and Hepatology*. 2009 Dec;7(12):1328-34.
14. Shields HM, Nambudiri VE, **Leffler DA**, Akileswaran C, Gurrola ER, Jimenez R, Saltzman A, Samuel PA, Wong K, White Iii AA, Hafler JP, Hayward JN, Pelletier SR, O'Farrell RP, Blanco PG, Kappler SM, Llerena-Quinn R. Using Medical Students to Enhance Curricular Integration of Cross-Cultural Content. *Kaohsiung J Med Sci*. 2009 Sep;25(9):493-502.
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3. **Leffler D**, Magallon J, Najar Goldar-Najafi A, Feller-Kopman D, Kelly CP. A Hidden Danger. Sepsis in Celiac Disease, case report and review of the literature. *Hospital Physician*. 2006 Oct;42(10):21-26

Invited Reviews, Chapters, and Editorials

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2. **Leffler D**, Kelly C. Update on the Evaluation and Diagnosis of Celiac Disease. *Curr Opin Allergy Clin Immunol*. 2006 Jun;6(3):191-6.
3. Gill B, **Leffler D**. Celiac Disease: Diagnosis, Autoimmune Mechanisms and Treatment. *Expert Review of Clinical Immunology*. September 2007, Vol. 3, No. 5, Pages 763-772
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5. **Leffler D**, Cheifetz, A. Forecasting the recurrence of ulcerative colitis: can U.C. the future? *Inflamm Bowel Dis*. 2008 Mar;14(3):422-4. Erratum in: *Inflamm Bowel Dis*. 2009 Feb;15(2):320.
6. **Leffler D**, Kelly CP. Celiac Disease: What The Last Few Years Have Taught Us. Advances in Digestive Disease. AGA Institute Press. Edited by Colin W. Howden. 2007
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8. **Leffler D**, Lamont JT. A 69 Year Old Female Presenting to the Hospital with 48 Hours of Abdominal Pain and Diarrhea: Educational Practice on *Clostridium difficile*. *Clinical Gastroenterology and Hepatology*. 2009 Oct;7(10):1046-8
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12. Germansky KA, **Leffler DA**. Development of Quality Measures for Monitoring and Improving Care in Gastroenterology. *Best Practice & Research: Clinical Gastroenterology*. 2011 Jun;25(3):387-95
13. **Leffler DA**, Cardenas A, Kelly CP. Celiac Disease. *Clinical Gastroenterology and Hepatology: The Modern Clinicians' Guide* Edited by Weinstein, Hawkey, and Bosch, Elsevier Science Press, 2011
14. **Leffler DA**. Clinical Crossroads: A 46 Year Old Female with Celiac Disease. *JAMA* 2011 Oct 12;306(14):1582-92.
15. **Leffler DA**, Lamont JT. Not So Nosocomial Anymore: The Growing Threat of Community Acquired *Clostridium difficile*. *American Journal of Gastroenterology*. 2012 Jan;107(1):96-8.
16. Martinez FJ, **Leffler DA**, Kelly CP. *Clostridium difficile* outbreaks: prevention and treatment strategies. *Risk Manag Health Policy*. 2012;5:55-64.
17. Mukherjee R, Kelly CP, **Leffler DA**. Gastrointestinal cancer in celiac disease: "the first days are the hardest days, don't you worry anymore?". *Clin Gastroenterol Hepatol*. 2012;Jan;10(1):4-6 [Editorial]
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19. Nasr I, **Leffler DA**, Ciclitira PJ. Management of Celiac Disease. *Gastrointest Endosc Clin N Am*. 2012 Oct;22(4):695-704.
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21. Mukherjee R, **Leffler DA**. Diseases of the Small Intestine. *Digestive Diseases Self-Education Program (DDSEP) 7*. American Gastroenterology Association. 2013
22. Vanga R, **Leffler DA**. Gluten sensitivity: not celiac and not certain. *Gastroenterology*. 2013 Aug;145(2):276-9. [Editorial]
23. Theethira TG, Dennis M, **Leffler DA**. Nutritional consequences of celiac disease and the gluten-free diet. *Expert Rev Gastroenterol Hepatol*. 2014 Feb;8(2):123-9.
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 32. **Leffler D.A.**, Dennis M., and Kelly C.P. Celiac disease. In D.K. Podolsky, M. Camilleri, J.G. Fitz, A.N. Kalloo, F. Shanahan, and T.C. Wang (eds) 2016, Celiac Disease Yamada's Textbook of Gastroenterology, 6th ed. Oxford: John Wiley & Sons, Ltd. pp 1264–1275.
 33. Mukherjee R, **Leffler DA**. Diseases of the Small Intestine. Digestive Diseases Self-Education Program (DDSEP) 8. American Gastroenterology Association. 2016
 34. **Leffler DA**, Green PH, Fasano A. Extraintestinal manifestations of coeliac disease. *Nat Rev Gastroenterol Hepatol*. 2015 Oct;12(10):561-71.
 35. Tapper EB, **Leffler DA**. The Morbidity and Mortality Conference in Gastroenterology and Hepatology: An Important Cornerstone of Patient Safety and Optimal Care. *Gastroenterology*. 2015 Nov 22. PMID: 26615118
 36. Silvester JA, **Leffler DA**. Recent Advances in Celiac Disease from TTG to Gluten in Pee. *Clin Transl Gastroenterol*. 2015 Nov 12;6:e125. PMID: 26561989
 37. Wungjiranirun M, Kelly CP, **Leffler DA**. Current Status of Celiac Disease Drug Development. *Am J Gastroenterol*. 2016 Mar 29. Review. PMID: 27021196

Non-peer reviewed scientific or medical publications/materials in print or other media

1. **Leffler D**, Cloud J, Kelly C. Letter in response to: Sandra Dial; J. A. C. Delaney; Alan N. Barkun; Samy Suissa. Use of Gastric Acid-Suppressive Agents and the Risk of Community-Acquired *Clostridium difficile*-Associated Disease *JAMA*, December 21, 2005; 294: 2989 - 2995. *JAMA* 2006 Jun 14;295(22):2599-600 [Letter to the Editor]
2. **Leffler D**. 'Getting Serious About Celiac Disease' Online Editorial for the American Gastroenterological Association. <http://www.gastro.org/journals-publications/aga-perspectives/getting-serious-about-celiac-2010> [Invited editorial]
3. **Leffler D**. 'The Vicious Cycle of Unrecognized Celiac Disease' Editorial for Gastroenterological Association publication *AGA Perspectives*. 7(1)2011
4. Kabbani TA, **Leffler DA**. Letter: rising incidence of obesity in the coeliac population - a malady or maladaptation? Authors' reply. *Aliment Pharmacol Ther* (2012 Jun) 35(12):1484 [Letter to the Editor]

5. Feuerstein JD, **Leffler DA**, Cheifetz AS. How physicians interpret research funding disclosures. NEJM. 2012 Dec 13;367(24):2358-9 [Letter to the Editor]
6. Feuerstein JD, **Leffler DA**. Colonoscopy and polyp characteristics. Ann Intern Med. 2013 Jan 15;158(2):141-2 [Letter to the Editor]
7. Kelly CP, Green PH, Murray JA, Dimarino A, Colatrella A, **Leffler DA**, Alexander T, Arsenescu R, Leon F, Jiang JG, Arterburn LA, Paterson BM, Fedorak RN; for the Larazotide Acetate Celiac Disease Study Group. Commentary: larazotide acetate - an exciting new development for coeliac patients? Authors' reply. Aliment Pharmacol Ther. 2013 Feb;37(4):496-497. [Letter to the Editor]
8. Feuerstein JD, **Leffler DA**, Cheifetz AS. Letter: international IBD practice guidelines - authors' reply. Aliment Pharmacol Ther. 2013 Aug;38(3):326-7. [Letter to the Editor]
9. Feuerstein JD, **Leffler DA**, Cheifetz AS. Letter: inflammatory bowel disease guidelines and conflicts of interest - authors' reply. Aliment Pharmacol Ther. 2013 Aug;38(4):445-6. [Letter to the Editor]
10. Bukoye B, **Leffler D**. Topical anesthetic-induced methemoglobinemia and veterans affairs hospitals-reply. JAMA Intern Med. 2013 Nov 25;173(21):2013-4. [Letter to the Editor]
11. Feuerstein JD, **Leffler DA**. Acute gastrointestinal bleeding. Ann Intern Med. 2013 Dec 3;159(11):793. [Letter to the Editor]
12. Rupa Mukherjee, **Daniel A. Leffler**. Digestive Diseases Self-Education Program (DDSEP) 7th edition. Chapter on small intestinal diseases - print and online published by the American Gastroenterological Association 2013[Book Chapter]
13. Natalia E. Castillo, **Daniel A. Leffler**. The Value of BCG and TNF in Autoimmunity. Editor Denise L. Faustman. Academic Press, March 2014 [Book Chapter]
14. Rohini Vanga, **Daniel A. Leffler**. GI/Liver Secrets 5th Edition. Editor Peter R. McNally. Chapter on celiac disease and small intestinal diseases. Elsevier Press 2014 [Book Chapter]
15. **Daniel A. Leffler**, Ciaran P. Kelly. Yamada's Textbook of Gastroenterology. 6th Edition. Chapter on celiac disease. Wiley Blackwell Press. 2014 [Book Chapter]
16. Kabbani TA, Vanga RR, **Leffler DA**, Villafuerte J, Pallav K, Hansen J, Mukherjee R, Dennis M, Kelly C. Response to aziz et Al. Am J Gastroenterol. 2014 Sep;109(9):1499-500. PMID:25196881 [Letter to the Editor]
17. Feuerstein JD, **Leffler DA**, Cheifetz AS. Colonoscopy is appropriately utilized in most cases following a fair bowel prep. Am J Gastroenterol. 2014 Aug;109(8):1289. PMID: 25091247[Letter to the Editor]

Professional educational materials or reports, in print or other media

1. 2005-2008 Tutorial Cases for *Gastrointestinal Pathophysiology Course 708.0* - Worked with Drs. Helen Shields and Antoinette Peters on development of the GI pathophysiology tutorial cases to include issues of culturally competent care for second year Harvard medical and dental students.
2. 2005 Hereditary Colorectal Cancer, A Practical Review - web content
Web based learning module of hereditary colon cancer for second year Harvard medical and dental students: http://ecommons.med.harvard.edu/VResources/getResources.aspx?a=&course_id=1003093377
3. 2006 Summary of Gastrointestinal Hormones handout
Creation of learning aid for gastrointestinal hormones as part of the GI pathophysiology course for second year Harvard medical and dental students

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4. 2006 'Some thoughts on a future in Gastroenterology' handout
Creation of a handout describing the training, research and employment opportunities for students interested in gastroenterology for second year Harvard medical and dental students
5. 2006 Integration of cross cultural care into problem based learning module - video
With Drs. Helen Shields and Antoinette Peters, I created a video demonstration of the integration of social and cultural issues in to a GI pathophysiology tutorial session for tutorial leaders and course instructors at Harvard Medical School
6. 2006 Oral Manifestations of Gastrointestinal Disease - web content
Web based review of oral manifestations of gastrointestinal diseases for second year Harvard medical and dental students [website no longer active]
7. 2009 Celiac Disease: Update on Diagnosis and Treatment - web content
Online CME course through Harvard Medical School Department of Continuing Education for physicians and other health care professionals
8. 2010 Nutritional Management of Celiac Disease - online slide set
Online CME course through the American Gastroenterological Association for Gastroenterologists
9. 2010 Defining Diagnosing and Managing Celiac Disease - Online slide set
Online CME course through the National Foundation for Celiac Awareness for Physicians and other health care professionals

Clinical Guidelines and Reports

1. 2006 1) Celiac Disease Diagnostic Algorithm
2) Celiac Disease Management Algorithm
Guidelines to standardize and improve the diagnostic approach to celiac disease
BIDMC Celiac Center Clinical Guidelines
2. 2007 1) Celiac Disease (Written with Dr. Ciaran Kelly)
2007 2) Chronic Diarrhea (Written with Dr. Ciaran Kelly)
2009 3) Zinc Deficiency
British Medical Journal; Point-of-Care Physicians Reference Database
Web based reference database focused on disease diagnosis and management. Updated annually
3. 2014 Shields HM, Atlas JS, **Leffler D**, Percac-Lima S, Sequist T, Chung D, Lim R, Roseto J, Ryou M. Prevention and Early Detection of Colorectal Cancer, A CRICO Decision Support Tool, 2014.

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1. Tariq S, Pallav K, Hansen J, Schuppan D, Kelly CP, **Leffler DA**. The Clinical Utility of HLA Testing in Celiac Disease Differential Diagnosis Digestive Diseases Week 2011

2. Pallav K, Tariq S, Daniel A. **Leffler DA**, Dennis M, Hansen J, Peer A, Schuppan D, Kelly CP. Serum IgA in Celiac Disease: The Unrecognized Importance of Partial IgA Deficiency. Digestive Diseases Week 2011
3. Na X, Martin A, **Leffler DA**, Flores SL, Lorraine K, Hu M, Kelly CP. Derivation and Validation of a Clinical Prediction Tool for Severe Clostridium difficile Infection Digestive Diseases Week 2011
4. Socioeconomic Status Influences Celiac Disease Diagnosis Mehra S, **Leffler DA**, Pallav K, Tariq S, Shah S, Green PH, Hansen J, Dennis M, Kelly CP Digestive Diseases Week 2011
5. Akbari M, Shah S, Kelly CP, Bhansali A, Hansen J, Dennis M, **Leffler DA**. Factors Affecting the Treatment Burden of Celiac Disease Digestive Diseases Week 2012
6. Akbari M, Shah S, Kelly CP, Bhansali A, Hansen J, Dennis M, **Leffler DA**. Socioeconomic Risk Factors for Celiac Disease Burden and Symptoms Digestive Diseases Week 2012
7. Kabbani TA, **Leffler DA**, Pallav K, Bhansali A, Dennis M, Kelly CP. Is Celiac Disease Protective Against Non-Insulin Dependent Diabetes Mellitus? Digestive Diseases Week 2012
8. Shah S, Akbari M, Kelly CP, Bhansali A, Hansen J, Dennis M, **Leffler DA**. Celiac Disease Has Higher Treatment Burden Than Common Medical Conditions Digestive Diseases Week 2012
9. Hsieh TT, Katchar K, Perera PN, Chen X, Xu H, Herzig SJ, **Leffler DA**, Kelly CP. Role of Ethnicity and IL-8 Polymorphisms in Clostridium difficile Susceptibility Digestive Diseases Week 2012
10. Ketwaroo GA, Tewani SK, Kheraj R, Raptopoulos V, **Leffler DA**. Mesenteric CT Angiography in the Evaluation and Management of Acute Lower GI Bleeding Digestive Diseases Week 2012

Narrative Report

My master's degree in nutrition, obtained from Columbia University prior to entering medical school, provided me with a strong background in the impact of nutrition on health and research methodologies which I have leveraged in my clinical and research career in gastroenterology. During my fellowship in Gastroenterology, I co-founded the Celiac Center at BIDMC and after graduation took on the role of Director of Clinical Research. Since then I have spearheaded numerous studies evaluating clinical outcomes and investigating new potential therapies for celiac disease and developing initiatives to improve patient care. This work has helped us to become one of the largest celiac disease centers in North America. Our multidisciplinary team currently cares for over 2000 patients with celiac disease and other gluten related disorders and is growing by approximately 15% annually.

Currently, I devote 20% of my time to clinical and teaching activities, 30% to research in celiac disease, and 50% to administration duties (20% celiac center and 30% gastroenterology/internal medicine administrative

and quality improvement efforts). Because of my patient centered focus in celiac disease and my work in quality improvement, I believe my area of excellence lies in clinical expertise and innovation.

Clinical expertise and innovation

My main focus in clinical innovation relates to Patient Safety and Quality Improvement where I am active as Director of Quality Improvement for the Division of Gastroenterology, Associate Director of Research for Quality Improvement in the Department of Medicine, a member of the Medical Peer Review Committee, Interventional Procedures Committee, and the Department of Medicine QI Leadership Council; and, most recently I elected to the Patient Safety Core Faculty of the Department of Medicine. I have been able to leverage my clinical research and QI skills to design and execute multiple effective interventions which have been published in high level peer reviewed journals including Archives of Internal Medicine, Gastroenterology and Gastrointestinal Endoscopy. I am co-director of the patient safety and quality improvement curriculum across medicine sub-specialty fellowships at BIDMC and am engaged in a range of patient safety and quality improvement initiatives working closely with the Silverman Institute for Health Care Quality & Safety and the Center for Healthcare Delivery, both at BIDMC. Projects have included development of a multi-disciplinary clinical care algorithm for management of gastrointestinal hemorrhage, a system for improving adherence to follow up recommendations in gastrointestinal endoscopy, and ongoing work on peri-procedural anticoagulation management and quality improvement in procedural sedation. This work has led to regional and national recognition and I currently am a member of the CRICO-RMF task force on colorectal cancer prevention and have published invited reviews of quality improvement in leading gastroenterology journals.

Contributions to Teaching and Education

Committed to the academic mission at BIDMC, I am an active participant in medical education, teaching the second year Harvard Medical School Gastrointestinal Pathophysiology Course for the past seven years and I was also the teaching fellow in 2006 working closely with Dr. Helen Shields on all aspects of course development and implementation. My specific focus in the course was the integration of cross cultural care into the problem-based learning sessions and the development of numerous novel educational tools and initiation of popular board-style quiz sessions. Through this work I earned an Excellence in Tutoring Award from the HMS Academy Center for Teaching and Learning and a nomination for the Excellence in Mentoring Award from the HMS Office of Diversity and Community Partnership. Most recently as part of my role on the Patient Safety Core Faculty at BIDMC, along with Dr. Anjala Tess, I am leading a series of training courses on patient safety and quality improvement for all clinical fellows in Department of Medicine fellowship programs at BIDMC. I also serve as Director of the Fellowship Program of the Celiac Center where I am responsible for selection, clinical oversight and mentoring of fellows in our celiac disease fellowship.

Significant Supporting Activities: Research

My efforts in celiac disease span both clinical and translational areas involving clinical outcomes and the development of novel non-invasive tests of celiac disease activity including the creation of disease specific survey tools assessing diet adherence, symptoms, and quality of life. The survey instruments in particular are used worldwide and have been translated into a number of languages. I am currently the PI on a K23 grant

assessing non-invasive markers of celiac disease activity, with a related R03 and R01 in review. I am also a close collaborator with both Dr. Detlef Schuppan in his work elucidating basic immunologic mechanisms of celiac disease, and with the celiac group at Children's Hospital. In addition, I am currently the PI on multiple industry-sponsored studies creating and evaluating celiac disease study outcomes and potential therapies. I have served as the Celiac Center Fellowship Director since 2010 and we currently train two fellows per year in a 1-2 year research and clinical training program. Papers I have authored on celiac disease have been published in top peer reviewed journals including JAMA, Gastroenterology, Gut and the American Journal of Gastroenterology. My book on celiac disease, *'Real Life with Celiac Disease: Troubleshooting and Thriving Gluten Free'* was published by the American Gastroenterological Association Press in May 2010, won an 'Indie Book Award' in 2011 and currently is rated 4.9 out of 5 stars on Amazon. Finally, my work in celiac disease has led to both national and international recognition and I currently serve as the secretary for The North American Society for the Study of Celiac Disease (www.nasscd.org), and on the international 'Oslo Group' developing consensus statements for celiac disease and related disorders.

Significant Supporting Activities: Administration

Administrative duties support the quality improvement initiatives and celiac center activities and are noted in detail above. Briefly, relating to quality improvement and patient safety, I serve on multiple department of medicine and hospital wide committees and am the Director of Quality Improvement for the Division of Gastroenterology. For the Celiac Center at BIDMC, I serve as the fellowship director as well as the Director of Clinical Research.

In conclusion, over the coming years I intend to continue to devote the majority of my time to clinical and translational research in celiac disease and patient safety and quality improvement initiatives central to the mission of BIDMC. Along with these major pursuits, I will continue to balance important efforts in patient care and medical education.

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Medwatch reports and source files for Mfr Report #s

SU-2004-002638	DSM-2009-00204
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